Liver Metastases

Incidence, Treatment & Prognostic Factors

JAM de Ridder

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Colofon

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CHAPTER 1

General introduction and outline of this thesis

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Cancer refers to a variety of diseases, characterized by the development of abnormal cells that divide in an uncontrollable way. Cancer cells have the ability to infiltrate and destroy normal body tissue and one of its characteristics is the tendency to metastasize throughout the body. Cancer is the leading cause of death in the Netherlands, directly followed by cardiovascular and pulmonary diseases.

In almost all types of cancer, the liver is a common site for metastatic disease. Blood supply of the liver facilitates entrapment of circulating cancer cells, which can develop into liver metastases. This is known as: "*the mechanical or hemodynamic hypothesis*", and was first described by Ewing in 1928.[1] This hypothesis explains liver involvement particularly in gastrointestinal cancers as a result of the blood flow to the liver by the portal vein (Figure 1). However, circulatory patterns alone do not explain liver metastases development for every primary tumour.

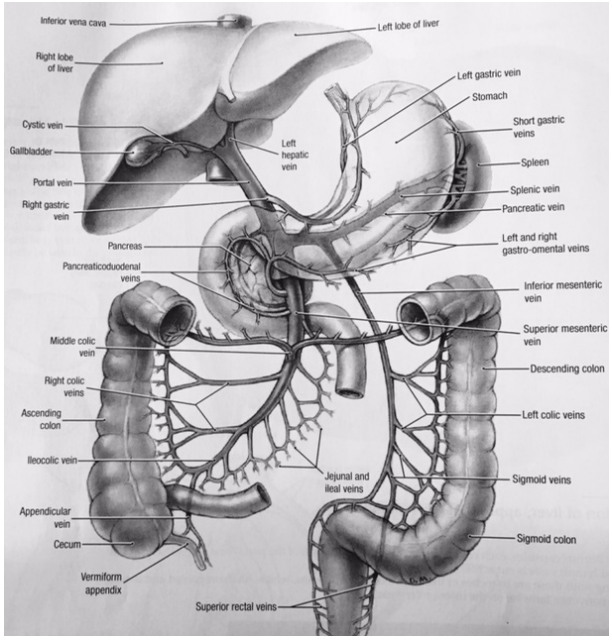

Figure 1. Blood supply to the liver by the portal system. Notice the drainage of the colon and small intestines by the colic, jejunal and ilial veins as well as the drainage of the upper gastrointestinal tract by the gastric, pancreatic and pancreaticoduodenal veins.

Some primary tumours selectively target the liver as a preferred metastatic location. Patients with uveal melanomas with a loss of chromosome 3 have such a predisposition for liver metastases.[2] Also in patients with breast cancer, different subtypes are associated with unique patterns of metastatic spread.[3] These two examples may be explained by the so-called "*seed and soil*" hypothesis, which presumes special molecular affinity for certain metastatic locations. *"The seeds of a plant are carried in all directions; but they can only live and grow if they fall on congenial soil"- Stephen Paget, 1889.*[4]

Incidences of liver metastases

As a result of the different mechanisms of metastatic spread and variable aggressiveness of primary tumours, incidences of liver metastases vary per primary tumour location.[5] Remarkably, there are limited modern data about the origins of liver metastases and their incidences. In order to explore the origins of liver metastases, a population based overview is presented in ***chapter 2***. This chapter provides population-based incidence data of histological confirmed liver metastases during the past 10 years in the Netherlands.

Liver resection for metastatic disease

In most cancer patients, the development of liver metastases is considered to be an incurable condition, and palliative systemic treatments will be proposed. However, for patients with certain tumour types (neuroendocrine carcinoma and colorectal cancer (CRC) in particular) liver resection is a known treatment option with curative intent.[6-8] Improvements in anesthetic techniques and post-operative care, led to decreased mortality rates after liver resection (<5%) in experienced liver surgery centers.[9-11] As a result, indications for liver resections are expanding, pushing the boundaries, and therefore more liver resections are carried out nowadays.[6,12] In ***chapter 3***, all liver resections for metastatic disease between 2001 and 2010 in the Netherlands, were analyzed. The primary aim of the study was to identify whether there was an increase in the number of liver resections, and in addition, it was explored whether trends in resection types or patient demographics during this decade could be identified. Furthermore, differences in liver resections were described between high and low volume centers.

For patients with colorectal liver metastases (CRLM) the only curative treatment option is liver resection, with a 5-year overall survival of approximately 50% in specialized liver centers.[6,7,13] In contrast, patients with non-colorectal liver metastases (non-CRLM) are rarely referred for surgery. Nevertheless, several small studies demonstrated an association between liver resection and improved survival in patients with non-colorectal liver metastases.[14-18] ***Chapter 4*** evaluates survival and prognostic factors after liver resection in patients with breast cancer liver metastases. This study aimed to identify possible risk factors and

prognostic factors for improved survival. ***Chapter 5*** describes a population-based evaluation of survival after liver resection of patients with metastatic melanoma.

Only a minority of patients with CRLM undergoes liver resection as part of their treatment. In the majority, liver resection is not possible due to the presence of extra-hepatic disease, or location, number or size of the liver metastases.[19,20]
In those cases of non-resectable CRLM treatment is limited to systemic therapy or palliative care. With the current combination of chemotherapy (fluoropyrimidines, oxaliplatin and irinotecan) and targeted agents (EGFR or VEGF antibodies), improvements in survival can be achieved with a median survival of 24 months. [21,22]
The outcome of modern systemic therapy in patients with resectable CRLM, without extrahepatic disease, is unknown, but relevant in the era of personalized medicine. Although liver resection is considered to be the gold standard treatment for patients with CRLM, it is questionable whether this is still the case with the improvements in systemic therapy regimens. **C*hapter 6*** aims to compare the survival of patients with resectable CRLM after either systemic therapy or liver resection in case-matched patient groups.

Risk assessment in patients with CRLM; patient selection
Cancer relapse is a common phenomenon even after a curative liver resection (R0), with approximately 50% of recurrences occurring in the first 2 years after the initial liver resection.[23] Various groups developed prognostic scoring systems to predict prognosis of patients with CRLM who were considered to be candidates for surgery. [20,24-27] The most used clinical risk score (CRS) was described by Fong *et al.*[28] and consists of five clinical factors and all of these factors can be assigned with one point if present as stated below. The total score is highly predictive for outcome after surgery.[29-31] The factors of the CRS[28] are presented in Table 1.

The selection of patients with CRLM who may benefit from surgery may improve further by the use of pre-operative fluorine-18-deoxyglucose positron emission tomography (FDG-PET).[32,33] It was hypothesized that patients where the FDG-PET scan did not identify extrahepatic disease were more likely to benefit from liver resection. This may be reflected in an improved disease-free and overall survival, compared to patients without preoperative staging with an FDG-PET scan. **C*hapter 7*** described the use of FDG-PET scans in the work-up of patients with CRLM. Survival was compared between patients with or without a pre-operative FDG-PET scans and patients were stratified by CRS.

Table 1. Clinical risk score according to Fong *et al.*[28]

Factor	0 points	1 point
Nodal status of the primary tumour	Lymph node-negative primary tumour	Lymph node-positive primary tumour
Interval between treatment of the primary tumour and detection of liver metastases	12 months or more	Less than 12 months
Size of the liver metastases	Smaller than 50mm	50 mm or larger
Number of liver metastases	Solitary liver metastasis	Multiple liver metastases
Carcinoembryonic antigen (CEA)	200ng/dl or less	More than 200ng/dl

In addition to clinical scoring systems and pre-operative FDG-PET scans, molecular and histopathological features of CRLM could have additional value in the prediction of prognosis after liver resection. For primary CRC many prognostic histological factors have been identified, and therapeutic decisions concerning adjuvant systemic therapy are made on these histopathological findings.[34] Usually, only two factors are described in the histological evaluation of metastatic lesions: confirmation of malignancy, and involvement of resection margins. A more detailed histological report of the liver metastases may have additional predictive value for prognosis. ***Chapter 8*** reviewed the literature of potential histopathological prognostic factors for improved survival in patients with CRLM. Most of the studies included in this review consisted of various histological parameters in heterogeneous patients groups. In order to identify reliable histological prognostic factors for overall survival in patients with CRLM after liver resection, ***chapter 9*** described a study in a homogeneous group of patients with solitary CRLM, without neo-adjuvant treatment. Liver resection specimens of these patients were reviewed and evaluated for several histopathological factors in combination with clinical prognostic factors, and associated with survival.

The summary of this thesis, concluding remarks and future aspects are described in ***chapter 10***.

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CHAPTER 2

Histologically confirmed liver metastases: a systematic analysis of 23,154 patients

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Abstract

Background: The liver is a common metastatic site for a large variety of primary tumours. For both patients with known and unknown primary tumours it is important to understand metastatic patterns to provide tailored therapies.

Objective: To perform a nationwide exploration of the origins of histological confirmed liver metastases.

Methods*:* Data were collected using the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). All histological confirmed liver metastases between January 2001 and December 2010 were evaluated for tumour type, origin of the primary tumour and were correlated with patient characteristics (age, gender).

Results: A total of 23,154 patients were identified. The majority of liver metastases were carcinomas (*n*=21,400; 92%) of which adenocarcinoma was the most frequent subtype (*n*=17,349; 75%). Most common primary tumours in patients with adenocarcinoma were from colorectal (*n*=8,004), pancreatic (*n*=1,755) or breast origin (*n*=1,415). In women of 50 years and younger, metastatic adenocarcinoma originated more frequently from breast cancer, while in women older than 70 years liver metastases originated more frequently from gastrointestinal tumours. Liver metastases in men older than 70 years originated often from squamous cell lung carcinoma. An unknown primary tumour was detected in 4,209 (18%) patients, although tumour type could be determined in 3,855 (92%) of them.

Conclusion: The current study provides an overview of the origins of liver metastases in a series of 23,154 patients.

Introduction

The liver is a common site for metastatic disease, however, little is known about the frequency in which various tumours present with liver metastases. Understanding these metastatic patterns is important for patients with a known primary tumour, as well as for patients with an unknown primary tumour. Knowledge of preferred metastatic sites in the first group of patients may direct staging and surveillance schemes, while in the group of patients with an unknown primary tumour the patterns can be used to predict the primary tumour site, which is important for treatment.

The high frequency of liver involvement in metastatic disease can be explained by the different hypotheses of metastatic spread. The double blood supply of the liver by the portal vein and the hepatic artery facilitates entrapment of circulating cancer cells, according to the "*mechanical or hemodynamic hypothesis*"[1], which explains the high incidence of liver metastases in patients with gastrointestinal carcinomas. However, some primary tumours selectively target the liver as a metastatic location, according to the *"seed-and-soil" hypothesis* [2]; examples are patients with uveal melanoma with a loss of chromosome 3 [3] , and patients with breast cancer with the human growth factor receptor 2 (HER-2) positivity in combination with estrogen (ER) and progesterone receptor (PR) positivity.[4]

Metastatic patterns in colorectal cancer have recently been evaluated in a large nationwide autopsy study, describing all autopsies between 1991-2010.[5] Hugen et al. demonstrated development of liver metastases in 32%-73% of the colorectal cancer patients, with significant differences between various histological subtypes. [5] While it is known that the majority of the liver metastases are of colorectal origin, exact data about incidences of non-colorectal liver metastases are scarce.
Large scale autopsy studies could potentially provide information, but these studies are rare, and often based on much older cohorts.[6, 7] An example is the study of DiSibio *et al.* which describes a cohort of autopsies between 1914 and 1943.[6] Since 1943 changes in both surgical treatment and adjuvant therapy are profound and likely to have influenced detection and development of liver metastases. To date, it remains unclear which primary tumours, other than colorectal cancer, metastasize to the liver and in which frequency they do so.

By analyzing all liver biopsies in an era of modern diagnostics and treatments, the incidences of liver metastases can be estimated for different primary tumours. This large scale, systematic, nationwide analysis of pathology reports generated between 2001 and 2010 showed new insights into the origins of liver metastases.

Methods

Patients and data collection

Data were collected using a search question in the PALGA-database; the nation-wide network and registry of histo-and cytopathology in the Netherlands. This network registers all pathology reports since 1971, with a nation-wide coverage since 1991.[8] With the key words; "liver metastases", "histology", and limited to the years "2001-2010", all pathology reports describing liver metastases were identified.

Pathology reports were excluded when patients underwent a liver resection or liver biopsy for a benign liver condition or for a primary malignant liver tumour such as hepatocellular carcinoma.

Per patient the following characteristics were collected from the pathology report: age and gender, the year of first histological diagnosis (in case of multiple biopsies, or a biopsy prior to liver resection), tumour type and subtype, and the location of the primary tumour.

For age three categories were used: 50 years and younger; between 51 and 70 years; and over 71 years. The patient's age at the first time of histological diagnosis was used in the analyses.

Tumour type and subtype were defined according to the International Classification of Disease (ICD-10). When the origin of the primary tumour was not described in the conclusion of the pathology report, additional reports of that patient were collected and evaluated to identify the primary tumour. When, after this assessment, no primary tumour could be detected, the primary tumour was classified as an "unknown primary". Anonymous data were used and both the privacy committee and scientific committee of PALGA approved the study design.

Statistical analyses

The chi-square test was used to compare nominal variables and the Mann-Whitney U test was used to compare continuous variables. A *p*-value of less than 0.05 was considered to be statistically significant. Multivariate regression analysis was used to determine differences in primary tumour locations between men and women in the age categories. All descriptive and statistical analyses were performed using statistical package for social sciences version 18.0 (SPSS, Inc., Chicago, Illinois, USA). Cytoscape version 3.2.1. was used to perform clock plots to visualize the origins of liver metastases of the carcinoma type. Circle size is the square root of the total number of liver metastases.

Results

General patient characteristics

During the study period, 24,136 pathology reports (20,098 liver biopsies and 4,038 liver resections) were retrieved. Double counts were excluded for 982 patients who underwent both a liver biopsy and liver surgery (*n*=390), patients who underwent multiple liver resections (*n*=342) or patients who underwent more than one liver biopsy (*n*=250). A total of 23,154 patients were included in the study (47% female). Median age at the time of liver biopsy was 67 years (range: 0-97 years), and 63 years (range: 1-91years) at the time of liver resection. The patients who underwent a liver biopsy at the age of 0 (*n*=3), were diagnosed with neuroblastoma, while the one-year old patient underwent a liver resection for metastatic Wilms tumour.

The amount of liver biopsies did not significantly increase over time. In 2001, 1,934 biopsies were performed, compared to 2,232 in 2010. In contrast, there was a significant decrease in pre-operative biopsies, from 10.8% in 2001 to 8.8% in 2010 ($p<0.001$). An increase of liver resections was observed; from 224 in 2001 to 596 in 2010 ($p<0.0001$).

Tumour types and organs of origin

Carcinoma was the most frequent tumour type, diagnosed in 21,400 patients (92.4%), followed by melanoma in 547 patients (2.4%), and sarcoma in 235 patients (1.0%). In 33 patients (0.1%) the tumour type was classified as 'other'. The pathologist was unable to define the tumour type of the liver metastases in 939 patients (4.1%) (Table 1).

Carcinoma

Adenocarcinoma not otherwise specified (N.O.S.) was the most frequent subtype of carcinoma (*n*=17,349;74.9%), followed by small cell carcinoma (*n*=1357,5.9%), neuroendocrine carcinoma (*n*=1072; 4.6%), large cell carcinoma (*n*=877; 3.7%), and squamous cell carcinoma (*n*=335; 1.4%) (Table 1).

Table 1. Tumour types and subtypes of liver metastases diagnosed by pathological evaluation.

Tumour type	Subtype	*n* (%)	Sex M (%)	F (%)	Median age y (range)
Carcinoma	**Total**	21400 (92.4%)	11397 (53.3%)	10003 (46.7%)	66 (17-97)
	Large cell carcinoma	877 (3.7%)	578 (65.9%)	299 (34.1%)	68 (1-90)
	Small cell carcinoma	1357 (5.9%)	851 (62.7%)	506 (37.3%)	69 (25-91)
	Squamous cell carcinoma	335 (1.4%)	199 (59.4%)	136 (40.6%)	65 (27-88)
	Transitional carcinoma	262 (1.2%)	199 (76.0%)	63 (24.0%)	69 (41-89)
	Adenocarcinoma N.O.S.	17349 (74.9%)	8892 (51.3%)	8457 (48.7%)	66 (20-97)
	Adenoid cystic carcinoma	5 (0%)	1 (20%)	4 (80%)	58 (40-63)
	Neuroendocrine carcinoma	1072 (4.6%)	590 (55.0%)	482 (45%)	65 (17-96)
	Merkel cell carcinoma	8 (0%)	6 (71.4%)	2 (28.6%)	72 (48-82)
	Renal cell carcinoma	102 (0.4%)	67 (65.7%)	35 (34.3%)	68 (37-87)
	Medullary carcinoma	16 (0.1%)	11 (68.8%)	5 (31.3%)	49 (17-73)
	Acinic cell carcinoma	1 (0%)	1 (100%)	0	31
	Thymic carcinoma	4 (0%)	2 (50%)	2 (50%)	53 (35-59)
	Granulosacell carcinoma	11 (0%)	0	11 (100%)	53 (39-71)
	Malignant mixed mullerian carcinoma	1 (0%)	0	1 (100%)	79
Melanoma	**Total**	547 (2.4%)	322 (58.9%)	225 (41.1%)	63 (20-88)
	Uveal	213 (0.9%)	123 (57.7%)	90 (42.3%)	65 (30-88)
	Cutaneous	251 (1.1%)	148 (59.0%)	103 (41.0%)	63 (20-87)
	Mucosal	5 (0%)	3 (60.0%)	2 (40.0%)	66 (51-80)
	Unknown primary	78 (0.3%)	48 (61.5%)	30 (38.5%)	61 (26-87)
Sarcoma	**Total**	235 (1.0%)	113 (48.5%)	122 (51.5%)	60 (3-86)
	Sarcoma N.O.S.	47 (0.2%)	21 (44.7%)	26 (55.3%)	61 (30-85)
	GIST	107 (0.5%)	63 (58.9%)	44 (41.1%)	62 (22-86)
	Angiosarcoma	3 (0%)	1 (33.3%)	2 (67.7%)	57 (3-75)
	Liposarcoma	3 (0%)	3 (100%)	0	59 (37-72)
	Leiomyosarcoma	64 (0.2%)	22 (34.4%)	42 (65.6%)	59 (33-85)
	Rhabdomyosarcoma	1 (0%)	0	1 (100%)	13
	Synoviasarcoma	2 (0%)	1 (50%)	1 (50%)	52 (41-93)
	Osteosarcoma	1 (0%)	1 (100%)	0	61
	Chondrosarcoma	2 (0%)	0	2 (100%)	72 (58-86)
	Ewing sarcoma	1 (0%)	0	1 (100%)	14
	Hemangiopericytoma	4 (0%)	1 (25%)	3 (75%)	45 (31-66)

Other	**Total**	33 (0.1%)	22 (67.7%)	11 (33.3%)	45 (0-76)
	Neuroblastoma	6 (0%)	1 (16.6%)	5 (83.3%)	0 (0-1)
	Nefroblastoma	3 (0%)	2 (67.7%)	1 (33.3%)	6 (5-37)
	Mesothelioma	6 (0%)	5 (83.3%)	1 (16.7%)	70 (55-76)
	Chordoma	1 (0%)	1 (100%)	0	72
	Ameloblastoma	1 (0%)	0	1 (100%)	50
	Insulinoma/glucagonoma	2 (0%)	1 (50%)	1 (50%)	65 (55-74)
	Brenner tumour	1 (0%)	0	1 (100%)	69
	Non-seminoma	2 (0%)	2 (100%)	0	26 (17-35)
	Germcell carcinoma	9 (0%)	8 (88.9%)	1 (11.1%)	33 (18-78)
	Choriocarcinoma	2 (0%)	2 (100%)	0	36 (22-50)
Unknown tumour type		939 (4.1%)	425 (45.2%)	514 (54.8%)	66 (1-90)
Total		23154 (100%)	12279 (53.0%)	10875 (47%)	66 (0-97)

N.O.S.: not otherwise specified

The majority of adenocarcinoma N.O.S. originated from the digestive tract (*n*=11,829; 68.2%), especially from colorectal origin (*n*=8,004; 46.1%). In 2,709 patients (15.6%), the primary tumour location was not specified (Figure1). For detailed information see Table 2.
Liver metastases of the small cell subtype were most often of pulmonary origin (*n*=1043; 76.9%). Primary tumour location was not specified in 268 patients (19.7%) (Table 2).
Neuroendocrine liver metastases originated most frequently from the digestive tract (*n*=389; 36.3%), especially from the pancreas (*n*=137; 12.8%) and duodenum (*n*=110; 10.3%). Pulmonary origin was observed in 238 patients (22.2%), and in 416 patients (38.8%) the primary tumour location was not specified (Table 2, Figure 1).
The primary tumour in large cell carcinoma liver metastases was most frequently located in the lung (*n*=305; 34.8%), followed by digestive tract (*n*=97; 11.1%) and urological tract (*n*=41; 4.7%). Primary tumour location was not specified in 376 patients (42.9%) (Table 2, Figure 1).
Squamous cell carcinoma liver metastases originated most often from the lung (*n*=118; 35.2%) or the digestive tract (*n*=66; 18.6%), more specifically from the esophagus (*n*=39; 11.6%). In 44 patients (12.4%) the primary tumour was located in the oropharynx. Primary tumour location was not specified in 72 patients (21.5%) (Table 2, Figure 1).

Table 2. Primary tumour locations in patients with histological confirmed liver metastases from adenocarcinoma; small cell carcinoma; neuroendocrine carcinoma; large cell carcinoma and squamous cell carcinoma.

		Adeno-carcinoma	Small cell carcinoma	Neuro-endocrine carcinoma	Large cell carcinoma	Squamous cell carcinoma
Head/Neck	**Total**	19 (0.1%)	-	2 (0.2%)	23 (2.6%)	46 (13.0)
	Pharynx/Larynx	8 (0%)	-	-	18 (2.1%)	44 (12.4%)
	Thymus	1 (0%)	-	-	3 (0.3%)	1 (0.3%)
	Thyroid gland	10 (0.1%)	-	2 (0.2%)	2 (0.2%)	1 (0.3%)
Digestive Tract	**Total**	11829 (68.2%)	24 (1.8%)	389 (36.3%)	97 (11.1%)	66 (18.6%)
	Colon/Rectum/Appendix	8004 (46.1%)	11 (0.8%)	86 (8.0%)	21 (2.4%)	7 (2.1%)
	Anus	2 (0.0%)	-	1 (0.1%)	1 (0.1%)	14 (4.2%)
	Stomach	507 (2.9%)	3 (0.2%)	13 (1.2%)	9 (1.0%)	1 (0.3%)
	Esophagus	349 (2.0%)	2 (0.1%)	3 (0.3%)	15 (1.7%)	39 (11.6%)
	Gall bladder/biliary tract	237 (1.4%)	2 (0.1%)	1 (0.1%)	7 (0.8%)	2 (0.6%)
	Pancreas	1755 (10.1%)	5 (0.4%)	137 (12.8%)	28 (3.2%)	2 (0.6%)
	Duodenum/small intestine	76 (0.4%)	-	110 (10.3%)	1 (0.1%)	1 (0.3%)
	N.O.S.	899 (5.2%)	1 (0.1%)	38 (3.5%)	15 (1.7%)	-
Lung		731 (4.2%)	1043 (76.9%)	238 (22.2%)	305 (34.8%)	118 (35.2%)
Skin		-	-	1 (0.1%)	1 (0.1%)	6 (1.8%)
Breast		1417 (8.2%)	2 (0.1%)	4 (0.4%)	24 (2.7%)	-
Gynecological tract	**Total**	314 (1.8%)	5 (0.3%)	7 (0.7%)	8 (0.9%)	26 (7.8%)
	Ovary	212 (1.2%)	3 (0.2%)	5 (0.5%)	3 (0.3%)	-
	Uterus	87 (0.5%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.6%)
	Cervix	15 (0.1%)	-	1 (0.1%)	4 (0.5%)	24 (7.2%)
Urological tract	**Total**	319 (1.8%)	15 (1.1%)	10 (1.0%)	41 (4.7%)	1 (0.3%)
	Kidney	144 (0.8%)	-	2 (0.2%)	9 (1.0%)	-
	Urinary bladder	20 (0.1%)	8 (0.6%)	3 (0.3%)	23 (2.7%)	1 (0.3%)
	Prostate	154 (0.9%)	7 (0.5%)	5 (0.5%)	7 (0.8%)	-
	Testis	1 (0%)	-	-	2 (0.2%)	-
Adrenal		6 (0%)	-	5 (0.5%)	2 (0.2%)	-
Other		5 (0%)	-	-	-	-
Unknown primary		2709 (15.6%)	268 (19.7%)	416 (38.8%)	376 (42.9%)	72 (21.5%)
Total		**17349**	**1357**	**1072**	**877**	**335**

N.O.S.: not otherwise specified.

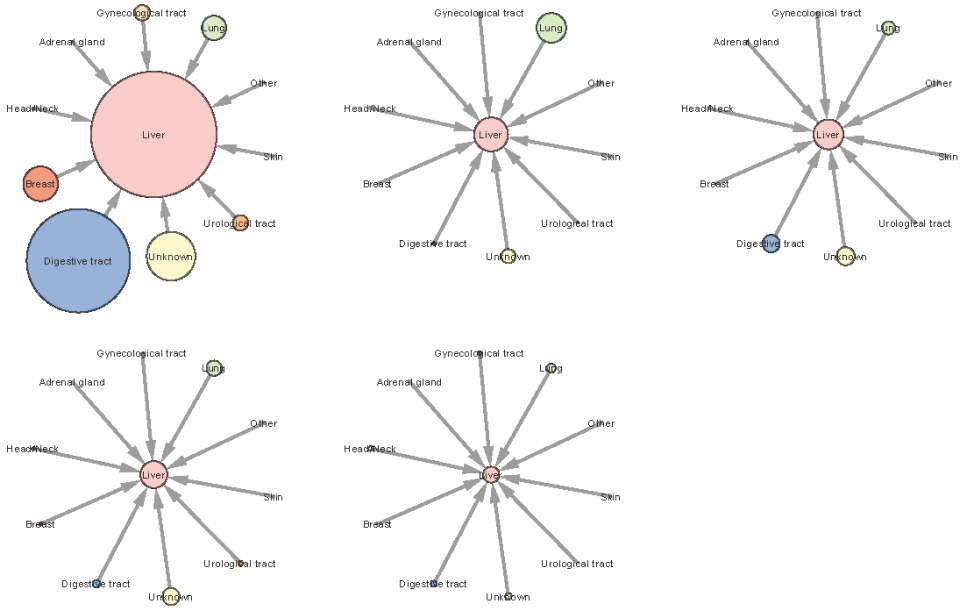

Figure 1. Origins of liver metastases of the carcinoma type. Each clock plot shows the origins of liver metastases per carcinoma subtype (adenocarcinoma, small cell carcinoma, neuroendocrine carcinoma, large cell carcinoma, squamous cell carcinoma). Outer circles represent the location of the primary tumour. Circle size is proportional to the numbers of metastases.

Melanoma

Metastatic melanoma was observed in 547 patients (2.4%) with liver metastases. Uveal melanoma was the primary tumour in 213 patients (38.9%), and primary cutaneous melanoma was the origin of liver metastases in 251 patients (45.8%). Liver metastases from mucosal melanoma were rare, with primary locations in the colon (*n*=3), small bowel (*n*=1), and urinary bladder (*n*=1). In 78 patients, the primary melanoma location was unknown (Table 1).

Sarcoma

Metastatic sarcoma was observed in 235 patients (1.0%) with liver metastases. The most prevalent subtype of metastatic sarcoma was gastrointestinal stromal tumour (GIST) (*n*=107; 45.5%), followed by leiomyosarcoma (*n*=64; 27.2%), and sarcoma N.O.S. (*n*=47; 20.0%) (Table 1).

For GIST metastases, the following primary locations were described; colon or rectum (*n*=8), stomach (*n*=48), small bowel (*n*=22), and digestive tract N.O.S. (*n*=10). In 18 reports the primary GIST location was not specified.

Primary tumour locations in patients with metastatic leiomyosarcoma were: colon (*n*=1), stomach (*n*=4), small bowel (*n*=6), uterus (*n*=14), ovary (*n*=1), kidney (*n*=2), bone/soft tissue

(*n*=33), or digestive tract (*n*=1). In 2 reports the location of the primary tumour location was not specified.
Primary tumour locations in patients with metastatic sarcoma N.O.S. were: bone/soft tissue (*n*=16); brain/meningeal (*n*=4); skin (*n*=2); rectum (*n*=1); oropharynx/nasopharynx (*n*=1) and small intestine (*n*=1). There was an unknown primary tumour location in 19 patients.

Gender differences in primary tumour locations
Histological confirmed liver metastases were more often observed in men than in women (*n*=12,280; 53.0% versus *n*=10,874; 47.0%; *p*<0.0001). Liver metastases from carcinoma (*n*=11,397; 53.3%; *p*=0.017), and melanoma (*n*=322; 58.9%; *p*=0.006) were more frequently diagnosed in men, whereas more women were diagnosed with liver metastases from an unknown tumour type (*n*=514; 54.8%; *p*<0.0001). In patients with liver metastases from carcinoma subtypes, male predominance was particularly observed in liver metastases with the subtypes: large cell carcinoma, small cell carcinoma, transitional carcinoma, and squamous cell carcinoma (Table 1, Figure 2).
Men presented relatively more often with liver metastases from colorectal adenocarcinoma compared to women [40.7% (*n*=4,625) versus 31.6% (*n*=3,379) (OR 1.63; 95%CI: 1.53-7.73; *p*<0.0001)].
Liver metastases from squamous cell lung carcinoma was more frequently observed in men than in women [45.7% (*n*=91) versus 19.9% (*n*=27) (95%CI: 2.052-5.638; *p*<0.0001)].

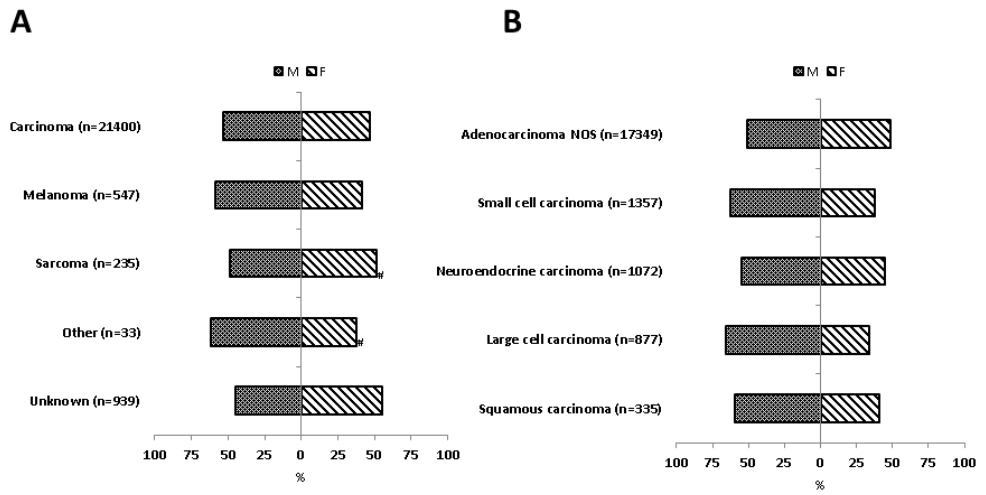

Figure 2. Differences in gender between tumour types. **(A)** and most important subtypes **(B)**. #: no significant gender differences.

Age differences

Most of the patients with liver metastases were older than 50 years (90.2%; *n*=20,892).

Metastatic adenocarcinoma from the digestive tract (including colorectal carcinoma liver metastases) were more common in older women (>70 years) than in younger women (≤50 [62.6% (*n*=1,823), versus 45.5% (*n*=540) (OR: 2.00; 95%CI: 1.75-2.30; *p*<0.0001)].

In contrast, a relative increased frequency of breast adenocarcinoma liver metastases was observed in younger women (≤50 years), compared to older women (>70 years) [34.2% (*n*=406) versus 8.9% (*n*=251) (OR 5.35; 95%CI 4.49-6.38; *p*<0.0001)]. There was no difference between young and older women in metastatic gynecological adenocarcinomas; 3.3% (age <50 years) versus 4.2% (age 51-70) versus 3.2% (age >70) (Figure 3a).

However, metastatic squamous cell carcinomas and metastatic neuroendocrine carcinomas from the gynecologic tract were more frequently observed in young women (≤50 years, compared to women older than 50 years [38.9% (*n*=7) versus 16.1% (*n*=19) (OR: 4.13; 95%CI: 1.47-11.57; *p*=0.007) respectively, 4.8% (*n*=3) versus 1.0% (*n*=4) (OR: 5.19; 95%CI: 1.13-23.75; *p*=0.034)] (Figure 3b and 3c).

Metastatic adenocarcinoma originated relatively more frequent from urological tumours in men, and especially in men older than 50 years [3.1% (*n*=249) versus 0.9% in younger men (≤50 years) (*n*=6) (OR: 3.7; 95%CI: 1.51-8.94; *p*=0.04)] (Figure 3a).

In older men (>70 years), liver metastases from squamous cell lung carcinoma were more frequent than in younger men (≤50 years) [46.4% (*n*=26) versus 18.1% (*n*=4) (OR: 3.90; 95%CI: 1.17-13.00; *p*=0.027)]; liver metastases from squamous cell lung carcinoma were most common in middle aged male patients (51-70 years) (*n*=61; 50.4%) (Figure 3c).

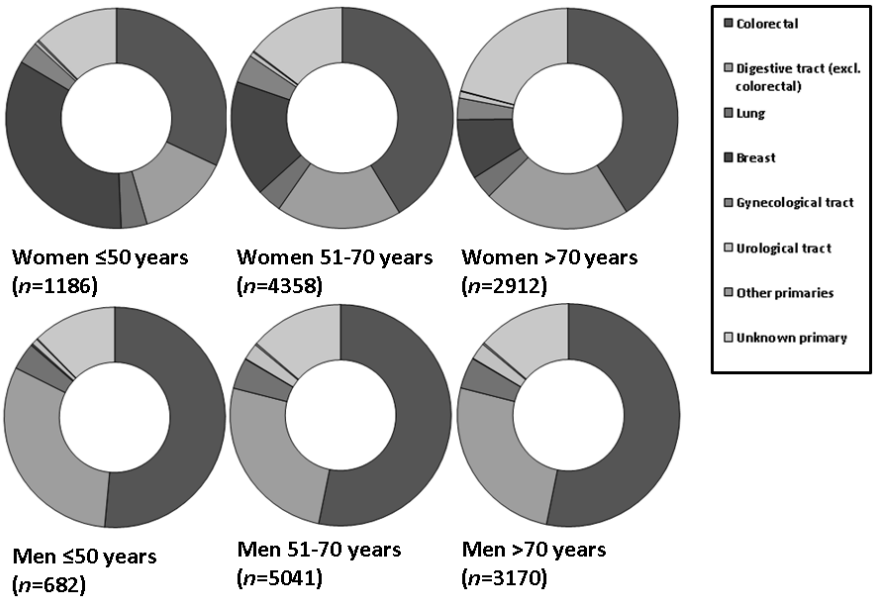

Figure 3A. Relative incidences of primary tumour locations in women and men with metastatic adenocarcinoma. In young women, metastatic breast cancer was more frequently observed (p<0.0001). Liver metastases from urological tumours were more frequently observed in men older than 50 years (p<0.0001).

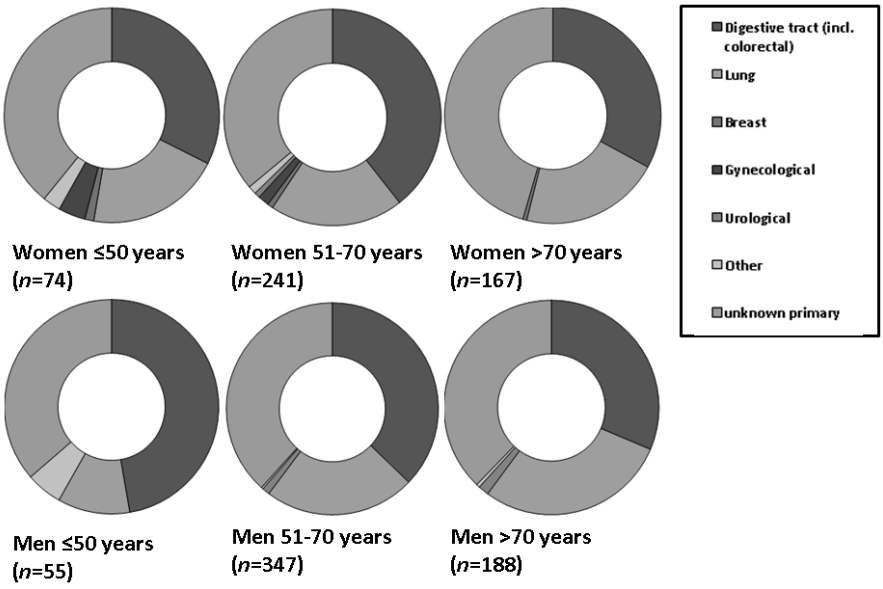

Figure 3B. Relative incidences of primary tumour location in women and men with metastatic neuroendocrine carcinoma. In young women (≤50 years), the primary tumour was significantly more often located in the gynecological tract (p=0.034).

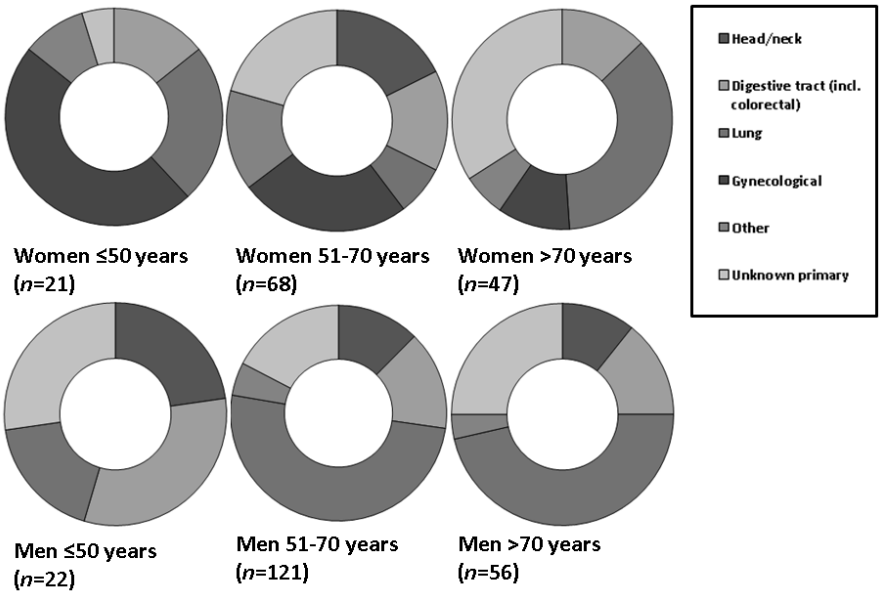

Figure 3C. Relative incidences of primary tumour locations in women and men with metatstatic squamous cell carcinoma. Liver metastases from the gynecological tract were more frequently observed in women ≤ 50 years (p=0.007). Primary tumour location in the lung was observed significantly more frequent in men older than 50 years (p=0.041).

Unknown primary tumours

After reviewing all pathology history and follow up, there were 4,317 patients (18.6%) without a primary tumour location. In most of these unsolved cases, tumour type was reported (n=3,963; 91.8%). Carcinoma was the most common tumour type (n=3,847; 89.1%), and the most prevalent tumour subtype was adenocarcinoma N.O.S. (n=2,709; 62.8%).

There was a small male predominance in patients with an unknown primary (n=2,262; 52.4%). Median age of patients with an unknown primary tumour was 68 years (range: 0-96 years). Patients with metastatic adenocarcinoma from an unknown primary tumour were significantly older at time of diagnosis, compared to patients with adenocarcinoma from a known primary tumour location; 68 years (range: 25-96 years) versus 66 years (range: 20-97 years) (p<0.0001). Median age of patients with an unknown primary from other tumour types and subtypes did not significantly differ from the age of patients with a known primary tumour.

Discussion

To the authors' knowledge, this is the first population-based study that describes the origins of histological confirmed liver metastases in a systematic way, including more than 23,000 patients during a 10-year time frame. The current study provides modern data on the origin and incidence of histological confirmed liver metastases from both biopsies and resection specimens in an era in which patients are treated according to modern standards.
Older cohort studies may represent a close approximation for the progression of untreated malignancies in humans,[6] but it is of no doubt that in time metastatic patterns of various malignancies have changed. In the autopsy study by DiSibio et al. the primary tumours that spread most frequently to the liver included testicular cancer and breast cancer.[6] In that cohort testicular cancer spread to the liver in 75% of the patients, while in the present study the amount of liver metastases from testicular cancer was almost negligible, partly due to the fact that these tumours are currently diagnosed with markers in blood or by using imaging techniques.[6] Moreover, with the current treatment of resection and systemic therapy, the prognosis of testicular cancer improved tremendously and as a result, histological confirmed liver metastases are diagnosed less frequently nowadays.[9, 10]
Reported incidences of breast cancer liver metastases also differed between autopsy studies and data of the present study.[6, 11] In time, a major improvement for breast cancer patients was made by the introduction of breast cancer screening programs. [12] In addition, changes in chemotherapy, post-operative radiotherapy and hormonal therapy resulted in improved prognosis and led to decreased incidences in breast cancer liver metastases.[6, 11, 13-15]

As to be expected, carcinoma was by far the most common tumour type (92%), more specifically adenocarcinoma N.O.S. (75%), found in patients with liver metastases. The most common primary tumour was colorectal carcinoma (35%). Liver resection was most often performed in patients with metastatic colorectal cancer, as was recently reported.[16]
In general, gender distribution of the primary tumours corresponded with gender distribution of the liver metastases, although some remarkable differences were observed. Liver metastases from thyroid cancer were more frequently diagnosed in male patients (51.3%) while, according to the Dutch National Cancer Registry, primary thyroid carcinoma is more prevalent in women (approximately 73% of all thyroid cancer types). Despite the small number of patients with liver metastases from thyroid cancer, this might suggest that the behavior of thyroid carcinoma in male patients is more aggressive, which is confirmed by a worse prognosis in male patients.[17] Similar findings were observed in male patients with liver metastases from cutaneous melanoma. Although primary cutaneous melanoma is more frequently observed in female patients (58.3%, according to the Dutch National Cancer Registry), male patients are more frequently diagnosed with liver metastases (59%). Again this seems to be the result of aggressive tumour behavior in male patients.[18,19]

The clinical value of the present data might be questioned, but they can be used in the process of clinical decision making. In patients with multiple primary tumours and liver metastases, an approximation of the relative frequency of liver metastases can be derived from the current study. This could guide additional diagnostic (e.g. biopsy, immohistochemistry) or treatment strategies (e.g. surgery, systemic therapy).
The current overview can also be used for clinical decision making in patients with cancer of an unknown primary tumour (CUP). CUP is defined as a presentation of histologically confirmed metastases, where, despite a standardized diagnostic approach, no primary tumour can be detected.[20] In 24%-50% of the patients with CUP liver metastases are found.[21-23] Understanding the pathophysiological and molecular biology is needed to improve selective treatment strategies, based on the primary tumour and in the end to improve survival in patients with CUP. The current large dataset might be a basis for further research in this group of patients.

Despite the size of this large, nation-wide population based study, selection bias should not be underestimated. Obviously, not all patients with liver metastases will undergo a liver biopsy. Especially in case of colorectal cancer liver metastases, the start of systemic treatment is often based on radiological diagnosis (CT-scan or FDG-PET scan) rather than on histological confirmation. Furthermore, although the liver is usually an easy access for biopsy, it is possible that histological or cytological confirmation was obtained from other metastatic sites such as: lymph nodes, ascites, pleural fluid, pulmonary lesions or any other metastatic location. Since these data and treatment, other than surgery, were not available in the current study, data on survival were not reported. On the other hand, many studies describe excellent results in patients diagnosed with liver metastases who underwent liver resection. This is not only the case in patients with colorectal cancer liver metastases, but improved survival has been reported in patients with other primary tumours, such as: breast cancer, melanoma, GIST or renal cell carcinoma.[24-27]

In conclusion, this study provides an overview of the origins of liver metastases, with regard to tumour type, age and gender, in an era of modern diagnostic and treatment modalities. These important data form a basis for future research, and can be used for the development of diagnostic strategies.

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CHAPTER 3

Liver resection for metastatic disease; a population-based analysis of trends

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Abstract

Objective: The study aims to evaluate all patients who underwent liver resection for metastatic disease for demographics, characteristics of the primary tumour and metastasis, volume of liver resection specimens per pathology laboratory, and to describe trends in surgical treatment.

Methods*:* Data were prospectively collected using the Dutch nationwide pathology network. All pathology reports containing details on liver resections for metastatic disease between January 2001 and December 2010 were evaluated.

Results: A total of 3,916 liver resections were performed in 3,699 patients with a median age of 63 years (range: 1–91). The primary tumour was mainly colorectal (*n* = 3,256; 88.0%). The number of 'high volume liver centers' increased from 2 to 12 in the study period, whereas the number of 'low volume centers' decreased. The number of liver resections increased from 224 to 596 per year ($p<0.0001$). A significant increase was demonstrated in elderly patients, patients with multiple metastases, liver resections for smaller metastases, and minor liver resections.

Conclusion: Although majority of patients were young and had solitary metastasis, indications for liver resection are expanding, as indicated by increasing numbers of elderly and patients with multiple liver metastases. Patients with non-colorectal liver metastases were seldom candidates for resection.

Introduction

Liver resection is considered standard treatment for patients with colorectal liver metastases (CRLM), with 5-year overall survival rates of 50% or more, depending on several clinical risk factors.[1-3] In addition, liver surgery is accepted as a treatment option in patients with neuroendocrine liver metastases (NELM), with a 5-year survival ranging from 60%-80%.[4-6] Selected patients with non-CRLM, non-NELM may also be potential candidates for surgical treatment, since several studies demonstrated an association with improved survival after liver resection.[7-12]

Improvements in anesthetic techniques and post-operative care led to decreased mortality rates of less than 3% in experienced liver surgery centers.[13-15] With these improvements, indications for liver resection are expanding and more patients with liver metastases undergo surgical treatment. [3, 16] Besides perioperative management improvements, innovations in surgical and non-surgical techniques; such as radio frequent ablation (RFA) therapy, portal vein embolisation, and availability of effective neo-adjuvant systemic therapies contribute to an increase in number of liver resections.[17, 18] In patients with initially irresectable CRLM, preoperative chemotherapy (often in combination with targeted agents such as bevacizumab and cetuximab) led to increased response rates and therefore to an increase of resectable CRLM.[19, 20] All of these factors are important and might contribute to the growing number of liver resections.

Population-based studies have described an increase in the amount of liver resections for metastatic disease, mainly in patients with colorectal cancer. In the UK, the number of patients who will undergo liver resection increased from 1.7% in 1998 to 3.8% in 2004.[21] A similar French study reported an increase in liver resection from 2-7% between 1976 and 1980 to 7-20% in the period between 1996 and 2000.[22] In both studies, only patients with liver metastases from colorectal origin were evaluated, and only few nationwide studies are available on liver resections performed for non-CRLM.[8, 10, 12]

The aim of this study is to assess changes in the number of liver resections carried out in both patients with CRLM, and non-CRLM. Different factors (e.g., number or size of metastases, patient age and tumour type) were evaluated during the study period to study potential differences in indication for liver surgery. Furthermore, the number of resection specimens per pathology laboratory was evaluated, in order to demonstrate the centralisation of liver surgery.

Methods

Patients and data collection

Data were collected using a query in the PALGA-database. This nationwide network and registry of histopathology and cytopathology in the Netherlands, has been collecting pathology reports since 1971, with a nationwide coverage since 1991.[23] The search terms: "liver metastases" and "histology" were used in the PALGA-database to identify all pathology reports containing details of liver metastases between January 2001 and December 2010. Patients who underwent liver resection for a primary liver malignancy or a benign liver lesion were excluded from this study. When the origin of the primary tumour was not described in the pathology report, all pathology reports of that specific patient were critically reviewed in order to obtain the origin of the primary tumour. Both the privacy committee and scientific committee of PALGA approved the study design.

The following characteristics were collected from the pathology reports per patient: year of liver resection, age at time of resection, gender, location of the primary tumour, tumour type, number and size of the liver metastases and the completeness of the resection.

Tumour typing was performed according to the International Classification of Diseases -10 (ICD-10). Neuroendocrine carcinoma included all types of neuroendocrine tumours (low and high grade). Primary tumours were classified according to the organ system of the primary tumour. Primary tumours were classified as 'not otherwise specified' (N.O.S.), if no definite origin was reported.

The type of liver resection was derived from the pathology report. A minor resection was defined as a resection of 3 or less liver segments. A major resection was defined as a resection of more than 3 liver segments. A re-resection was considered to be a scheduled 'two-stage procedure' when patients underwent a re-resection within 3 months after the initial liver resection. These procedures were classified by definition as major resections.
Liver resection was considered a complete resection (R0) when the pathologist described free resection margins. Details regarding distance of resection margins were not described in all pathology reports and therefore not recorded in the current study. The difference between microscopic incomplete (R1) and macroscopic incomplete resections (R2) was not always clearly reported, and therefore, both were analyzed as one group of incomplete resections. The size of the largest liver metastasis was reported in patients with multiple liver metastases.

Pathology reports in the PALGA database are registered anonymously, without details and names of the hospitals and surgeons which delivered the resection specimen. The pathology laboratories where the specimens were assessed were registered. Since all hospitals in the Netherlands where liver surgery is performed have their own pathology laboratory, the number of laboratories is a reliable reflection of the number of hospitals. Laboratories that examine one or less liver resection specimen per year were defined as 'incidental centers'. These centers were not included in the analyses of hospital volume. 'Low volume centers' were defined as laboratories which examine 2 to 9 liver resection specimens per year; laboratories which examine 10 to 19 liver resection specimens per year were defined as 'middle volume centers' and 'high volume centers' were defined as laboratories which examine more than 20 liver resection specimens yearly.

Statistics

The Mann-Whitney U test was used to compare medians between the group of patients with CRLM and the non-CRLM group. To compare nominal variables the Pearson chi-square test was used. Multivariate logistic regression analysis was used to determine the independent effect of the time period of diagnosis on the chance to undergo a liver resection. Stratification was carried out for size and number of metastases, type of resection and resection margins. Multivariate regression analysis was used to assess differences in tumour and patient characteristics between 'high', 'middle' and 'low volume centers'. A *p*-value of less than 0.05 was considered statistically significant. All descriptive and statistical analyses were performed using statistical package for social sciences version 18.0 (SPSS, Inc., Chicago, Illinois., USA).

Results

General patient characteristics

A total number of 24,138 pathology reports describing histologically confirmed liver metastases between 2001 and 2010, were identified and reviewed from the PALGA database. The majority of these reports (*n* = 20,222) described results of liver biopsies for metastatic disease and were excluded from the present study. The remaining 3,916 pathology reports described liver resections for metastatic disease and were included in the present study. Resections were performed in 3,699 patients (59% male and 41% female). During the study period, 203 patients (5.5%) underwent a re-resection and 14 patients underwent a third resection. Median age at the time of the primary liver resection was 63 years (range: 1-91 years). The 1-year old patient underwent liver resection for metastatic Wilms tumour.

Primary tumour characteristics

Most of the liver resections were performed in patients with metastatic carcinoma (*n* = 3,557; 96.2%), mostly located in the colon or rectum (*n* = 3,238; 82.7%). Metastatic melanoma (*n* = 36; 1.0%) and metastatic sarcoma (*n* = 46; 1.2%) were rare indications for liver resection (Table 1).

Table 1. Pathological evaluation of various tumour types found in initial liver resection specimens.

	n (%)	Sex		Age, years, median (range)
		Male	Female	
Carcinoma				
Total	3,557 (96.2%)	2114 (59.4%)	1443 (40.6%)	64 (17-91)
Adenocarcinoma N.O.S.	3,450 (97%)	2060 (59.7%)	1390 (40.3%)	64 (20-91)
Neuroendocrine carcinoma	55 (1.5%)	24 (43.6%)	31 (56.4%)	59 (17-79)
Squamous cell carcinoma	12 (0.3%)	4 (33.3%)	8 (66.7%)	54 (41-67)
Other	40 (1.2%)	26 (65.0%)	14 (35.0%)	57 (17-77)
Melanaoma				
Total	36 (1.0%)	21 (58.3%)	15 (41.7%)	52 (28-69)
Occular	11 (30.6%)	5 (45.5%)	6 (54.5%)	57 (34-66)
Cutaneous	14 (38.8%)	10 (71.4%)	4 (28.6%)	45 (39-69)
N.O.S.	11 (30.6%)	6 (54.5%)	5 (45.5%)	51 (28-66)
Sarcoma				
Total	46 (1.2%)	18 (39.1%)	28 (60.9%)	56 (3-75)
Sarcoma NOS	4	1 (25.0%)	3 (75.0%)	58 (30-69)
Angiosarcoma	1	-	1 (100%)	3
GIST	21	13 (61.9%)	8 (38.1%)	59 (24-74)
Leiomyosarcoma	18	4 (22.2%)	14 (77.6%)	56 (33-75)
Rhabdomyosarcoma	1	-	1 (100%)	13
Chondrosarcoma	1	-	1 (100%)	58
Other				
Total	6 (0.2%)	4 (66.7%)	2 (33.3%)	21 (5-37)
Nefroblastoma	1	-	1 (100%)	5
Germ cell tumour	4	3 (75%)	1 (25%)	28 (20-37)
Non-seminoma	1	1 (100%)	-	17
N.O.S.	54 (1.4%)	27 (50%)	27 (50%)	60 (1-83)
Total	3,699 (100%)	2,184 (59.0%)	1,515 (41.0%)	63 (1-91)

N.O.S.: not otherwise specified

Other locations of carcinomas are presented in Table 2. Tumour subtypes in CRLM from carcinoma, were adenocarcinoma N.O.S. (*n* = 3,224), neuroendocrine carcinoma (*n* = 11), and squamous cell carcinoma (*n* = 3). The tumour type was not reported in 15 patients with metastases from colorectal origin. In 3 patients, a GIST was diagnosed as the tumour subtype

in liver metastases originating from a colorectal primary tumour. Besides colon or rectum, other primary GIST locations were stomach (*n* = 7), duodenum or small intestine (*n* = 10), and digestive tract N.O.S. (*n* = 1).

Table 2. Primary tumour location in patients with liver metastases from carcinoma who underwent liver resection

	n	Sex, *n* (%)		Age, years, median (range)
		Male	Female	
Head/neck				
Total	12	9 (75.0%)	3 (25.0%)	49 (17-65)
Pharynx/Larynx	3	3 (100%)	-	56 (32-58)
Thymus	2	2 (100%)	-	44 (35-52)
Thyroid gland	7	4 (57.1%)	3 (42.9%)	48 (17-65)
Digestive system				
Total	3,391	2,065 (60.9%)	1,326 (39.1%)	64 (52-76)
Colon/Rectum/Appendix	3,238	1,983 (61.2%)	1,255 (38.8%)	64 (24-94)
Anus	3	1 (33.3%)	2 (66.7%)	53 (45-59)
Stomach	20	17 (85.0%)	3 (15.0%)	68 (36-79)
Esophagus	15	11 (73.3%)	4 (26.7%)	60 (35-73)
Gall bladder/biliary tract	22	7 (27.3%)	16 (72.7%)	66 (52-86)
Pancreas	51	28 (54.9%)	23 (45.1%)	62 (34-82)
Duodenum/Small intestine	25	9 (36.0%)	16 (100%)	59 (45-75)
N.O.S.	17	9 (52.9%)	8 (47.1%)	62 (38-86
Lung	7	4 (57.1%)	3 (42.9%)	64 (52-76)
Skin	1	-	1 (100%)	47
Breast	32	-	32 (100%)	51 (31-82)
Genital tract				
Total	39	0	39 (100%)	58 (28-85)
Ovary	35	-	35 (100%)	56 (28-85)
Uterus	2	-	2 (100%)	66 (61-71)
Cervix	2	-	2 (100%)	55 (51-58)
Urological tract				
Total	33	21 (63.6%)	12 (36.4%)	58 (31-82)
Kidney	26	15 (57.7%)	11 (42.3%)	65 (20-79)
Urinary bladder	4	3 (75.0%)	1 (25.0%)	68 (62-77)
Prostate	1	1 (100%)	-	61
Testis	2	2 (100%)	-	48 (27-68)
Adrenal	4	2 (100%)	2 (100%)	64 (59-68)
Other	2	1 (50%)	1 (50%)	64 (59-68)
N.O.S.	36	12 (33.3%)	24 (66.7%)	62 (17-79)
Total	3557	2114	1443	

N.O.S.: not otherwise specified

Patients who underwent liver resection for non-CRLM were younger at time of operation (median 59 years; range: 1-86 years) compared to patients with CRLM (median 64 years; range: 24-91 years; $p<0.0001$). Patients with CRLM were predominantly male (61.4%), whereas patients who underwent resection for non-CRLM were mostly female (58.1%; $p<0.0001$). Female predominance in patients with non-CRLM can be explained by 52 patients (11.9%) with metastatic gynecological tumours (cervix $n = 3$; uterus $n = 9$, and ovary $n = 40$) and 32 patients (7.2%) with metastatic breast carcinoma.

Liver resections

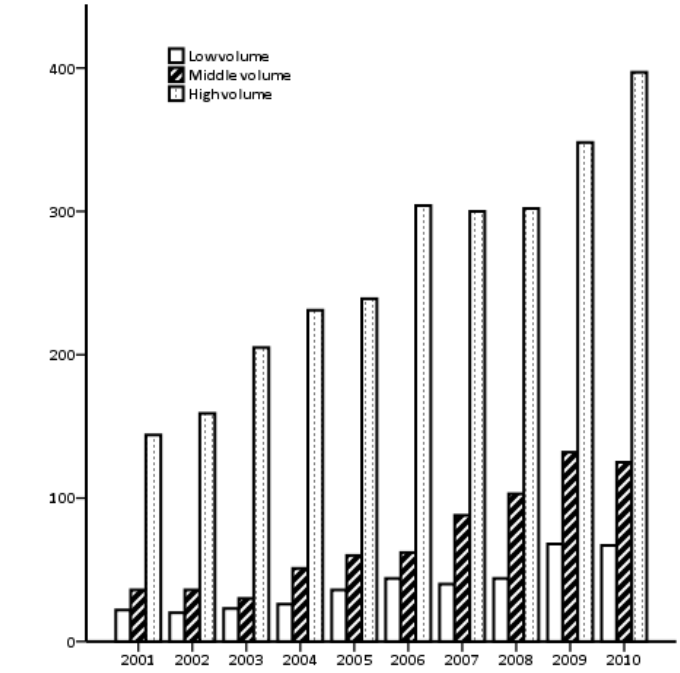
Minor resections were performed in 2,336 patients (59.7%), mostly a segmentectomy ($n = 1,483$; 63.5%). A non-anatomical resection was performed in 834 patients (35.7%). In 19 patients (0.8%) the resection type was not specified. Hemihepatectomy was performed in 974 patients (24.9%); right-sided hemihepatectomy in 572 patients (14.6%), left sided hemihepatectomy in 171 patients (4.4%), and 117 patients (3.0%) underwent an extended hemihepatectomy. The side of the hepatectomy was not specified in 114 patients (2.9%).
A complete resection (R0) was performed in 3,058 patients (78.1%), 482 patients (12.3%) underwent an incomplete resection (R1 or R2), and in 376 patients (9.6%) the resection margins were not described. The median number of resected metastases was 1 (range: 1-19) and the median size was 34.0 mm (range: 1-280 mm).

Re-resections and 'two-stage procedures'

During the study period, 203 patients (5.5%) underwent a re-resection, mostly for CRLM ($n = 183$; 95.3%). Eleven patients underwent a re-resection as part of an intended 'two-stage procedure', after a median of 42 days (range: 21-84 days) from the initial liver resection. The remaining 192 patients underwent a re-resection as a result of disease recurrence; 14 patients underwent a third liver resection. Patients who underwent a re-resection were significantly younger (median 61 years; range: 24-78 years), compared to patients who underwent a single liver resection (median 63 years; range: 1-91 years) ($p = 0.042$). The re-resection was performed after a median of 12 months (range: 3-73 months) from the initial liver resection.

Liver resections per pathology laboratory

The number of pathology laboratories examining liver resection specimens decreased from 37 in 2001 to 31 in 2010. Especially the 'low volume' and 'sporadic centers' decreased from 15 respectively 11 in 2001, to 10 respectively 2 in 2010 (Figure 1). A median of 28 resection specimens (range: 20-84) were evaluated annually in 'high volume centers'. 'Middle volume centers' examined 13 resection specimens (range: 10-19) per year, and in 'low volume centers' 4 resection specimens (range: 2-9) were evaluated yearly.



Nr of PA-labs:										
Low volume	15	14	19	20	17	18	15	16	7	10
Middle volume	9	6	3	4	8	4	5	7	13	7
High volume	2	4	6	6	5	9	9	9	10	12

Figure 1. Amount of liver resections performed in high (≥20 liver resections per year), middle (11-19 liver resections per year) and low volume centers (1-9 liver resections per year). Below the figure is the number of pathology (PA) laboratories involved in examining liver resection specimens per year.

In 'high volume centers', resection specimens with multiple metastases (OR 1.348; 95%-CI 1.069-1.701), and non-CRLM (OR 1.397; 95%-CI 1.216-3.452) were more often examined, than in 'middle' and 'low volume centers'. Furthermore, in 'high volume centers' patients were younger (<75 years) at the time of liver resection, compared to 'low' and 'middle volume centers' (OR 0.564; 95%-CI 0.423-0.754). No differences were observed in the amount of complete (R0) resections and in the size of the liver metastases between the 'high', 'middle' and 'low volume centers' (Table 3).

Table 3. Patterns in resection chracteristics in low (1-9 liver resections per year), middle (10-19 liver resections per year) and high volume centers (≥20 liver resections per year) (logistic regression)

	Low volume* (*n*=390)	**Middle volume (*n*=723)**	**High volume (*n*=2,629)**
Size			
≤50mm	111 (75.5%)	346 (82.0%)	1,201 (76.4%)
>50mm	36 (24.5%)	76 (18.0%)	371 (23.6%)
NR	243	301	1,057
OR (≤50mm vs. >50mm) (95%-CI)	-	1.477 (0.941-2.317)	1.050 (0.708-1.556)
Number of metastases			
Solitary	251 (67.8%)	443 (64.3%)	1,549 (61.0%)
Multiple	119 (32.2%)	246 (35.7%)	990 (39.0%)
NR	20	34	90
OR (multiple vs. solitary) (95%-CI)	-	1.171 (0.896-1.531)	**1.348 (1.069-1.701)****
Resection margins R0	305 (87.1%)	597 (90.3%)	2,064 (85.6%)
R1/2	45 (12.9%)	64 (9.7%)	348 (14.4%)
NR	40	62	217
OR (R1/2 vs. R0) (95%-CI)	-	0.727 (0.484-1.090)	1.143 (0.819-1.594)
Type of metastases			
Colorectal	354 (90.8%)	661 (91.4%)	2,302 (87.6%)
Non colorectal	36 (9.2%)	62 (8.6%)	327 (12.4%)
OR (CRLM vs. non-CRLM) (95%-CI)	-	0.922 (0.600-1.419)	**1.397 (1.216-3.452)****
Age			
<75 years	322 (82.6%)	629 (87.0%)	2,349 (89.3%)
≥75 years	68 (17.4%)	94 (13.0%)	280 (10.7%)
OR (<75 years vs. ≥75 years) (95%-CI)	-	0.708 (0.504-.994)	0.564 (0.423-0.754)

NR: not reported, Values are *n* (%) unless otherwise indicated. * Low volume center was the reference for logistic regression. ** In bold: Statistically significant

Trends in liver resections

The annual number of liver resections increased from 224 in 2001 to 596 in 2010 ($p<0.0001$). This increase was mainly due to an increase in liver resections for CRLM. The number of liver resections performed for non-CRLM remained almost stable (Figure 2). The percentage of re-resections increased not significantly, from 3.9% in the period between 2001 and 2004 to 5.0% between 2008 and 2010.

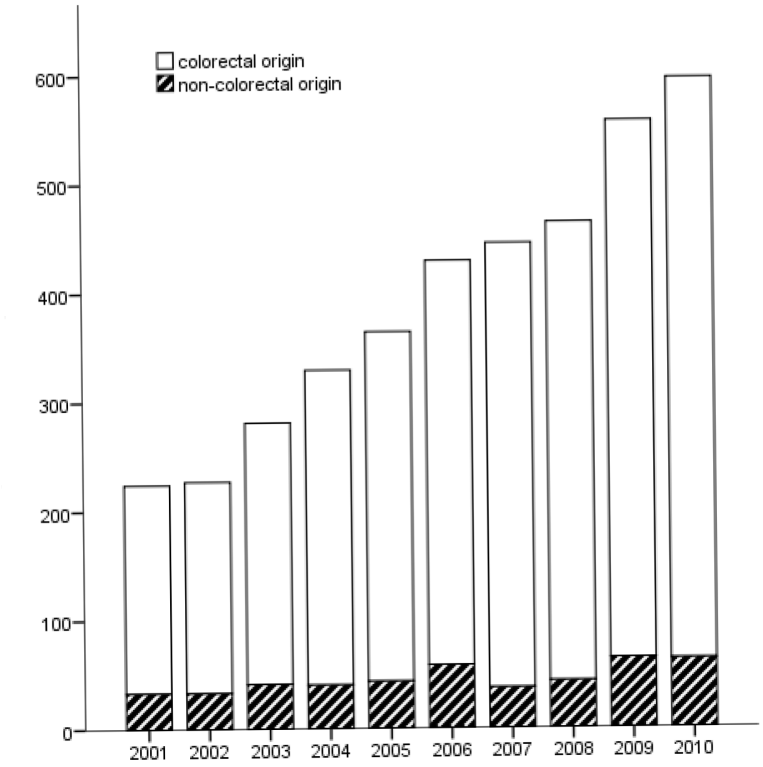


Figure 2. Number of liver resections per year performed for metastatic disease. On the X-axis the year of liver liver resection, and on the Y-axis the number of liver resections.

In 2001, the median age at the time of liver resection was 62 years (range: 1-85 years), which increased to a median age of 64 years (range: 28-89 years) in 2010 (p<0.0001). The higher age was also demonstrated by the percentage of elderly patients (> 75 years) who underwent liver resection. Between 2001 and 2004, 9.1% of the patients undergoing a liver resection were older than 75 years, which increased to 13.9% between 2008 and 2010 (OR 1.61; 95%CI: 1.25-2.07).

Between 2001 and 2004, liver resections were mainly performed for solitary metastasis (67.2%), which decreased to 60.5% between 2008 and 2010. In this time period, more liver resections were performed for multiple liver metastases (OR 1.34; 95%CI: 1.13-1.58) (Table 3).
During the study period, an increase in percentage of small metastases (≤ 50 mm) was demonstrated. In the period between 2001 and 2004, 70.8% of the metastases were 50 mm or smaller, which increased to 79.7% between 2008 and 2010 (OR 1.62; 95%CI: 1.27-2.07). This coincided with an increase in minor resections from 63.5% between 2001 and 2004 to 74.7% between 2008 and 2010 (OR 1.69; 95%CI: 1.41-2.03) (Table 4).

Table 4. Annual patterns in resection characteristics (logistic regression)

	2001-2004* (*n*=1,061)	**2005-2007 (*n*=1,238)**	**2008-2010 (*n*=1,617)**
Size			
≤50mm	364 (70.8%)	526 (79.1%)	798 (79.7%)
>50mm	150 (29.2%)	139 (20.9%)	203 (20.3%)
NR	547	573	616
OR (≤50mm vs. >50mm) (95%-CI)	-	**1.559 (1.194-2.036)****	**1.620 (1.268-2.069)****
Number of metastases			
Solitary	684 (67.2%)	761 (63.9%)	940 (60.5%)
Multiple	334 (32.8%)	429 (36.1%)	613 (39.5%)
NR	43	48	64
OR (multiple vs. solitary) (95%-CI)	-	1.154 (0.968-1.377)	**1.335 (1.132-1.576)****
Resection margins			
R0	796 (85.7%)	966 (87.1%)	1,296 (86.3%)
R1/2	133 (14.3%)	143 (12.9%)	206 (13.7%)
NR	132	129	115
OR (R1/2 vs. R0) (95%-CI)	-	0.886 (0.687-1.142)	0.951 (0.752-1.204)
Type of resection			
Minor	540 (63.5%)	730 (68.9%)	1,066 (74.5%)
Major	314 (36.5%)	332 (31.1%)	367 (25.5%)
NR	207	176	184
OR (major vs. minor) (95%-CI)	-	**1.279 (1.057-1.546)****	**1.689 (1.407-2.028)****

NR: not reported, Values are *n* (%) unless otherwise indicated. * 2001-2004 was the reference period for logistic regression. ** Statistically significant with *p*-value <0.05. Note that all patients who underwent a 2-staged procedure had multiple metastases and underwent a major resection.

Discussion

The current study describes all liver resections performed in the last decade for metastatic disease in the Netherlands. A significant increase in number of liver resections was demonstrated, predominantly in patients with CRLM. Part of this increase may be explained by the increasing incidence of primary colorectal carcinoma and, as a result, CRLM. Additional explanations for the increase in resections can be found in the expansion of indications for liver resection.

A significant increase in patients' age at the time of resection was demonstrated, as well as an increase in the percentage of elderly patients (>75 years). There is controversy in literature whether these elderly patients have an increased risk of post-operative complications and

mortality. Some reports state that complication rates may be increased, whereas others report similar complication rates irrespective of age.[24-26] The trend towards operating more elderly patients, as observed in the current study, suggests that age is not considered a contraindication for liver resection. Data on comorbidity and clinical condition of the patients were not available in the current study, but these factors may very well be more important in judging patients fit for surgery.

The percentage of patients with multiple liver metastases who underwent resection increased. Between 2001 and 2004, only 32.8% of the liver resections were performed for multiple metastases, which increased to 39.5% between 2008 and 2010. Until recently, surgery was usually only recommended for patients with up to three metastases, and no evidence of extrahepatic disease.[27] A recent meta-analysis reported no correlation between number of metastases and survival rates.[28] Nowadays, multiple liver metastases are less often considered a contraindication because of the emergence of effective neo-adjuvant systemic therapy [16], and improvements in surgical strategies. With combinations of portal vein embolisation [29], radiofrequent ablative (RFA) therapies [30] or two-staged resections [19, 31] more patients become eligible for liver resection.

Resected liver metastases were smaller in patients who underwent liver resection between 2008 and 2010 compared to the size of metastases resected between 2001 and 2004. Although data on neo-adjuvant systemic therapy were not available, increased neo-adjuvant treatment may be an explanation for the smaller metastases found in the resection specimens. Other explanations could be improved imaging techniques, or more rigorous follow-up schedules for patients suffering from colorectal cancer.

In the present study, there were no differences in the percentages of complete resections (R0) between high and low volume centers. There were also no differences in the number of R0 resections in patients during the study period. Due to the nature of the study and many different pathology laboratories where the liver resections were evaluated, it was impossible to discriminate between R1 and R2 resections. The exact free resection margin in millimeters was absent in many pathology reports; therefore, no definite conclusions could be drawn regarding exact resection margins.

Although increasing numbers of patients in the Netherlands undergo liver resection, still relatively few patients developing CRLM undergo liver surgery. Data from the national cancer registry show an incidence of colorectal carcinoma of 12,755 patients in 2010. In recent years 21-24% of patients with colorectal cancer presented with metastatic disease (M1) at the time of diagnosis, which is approximately 3000 patients per year .[32] [33] These

synchronous metastatic lesions are limited to the liver in approximately 55% of these patients (3,000*0.55=1,650 patients in Dutch population annually).[34] Recent data from the national cancer registry demonstrated that approximately 20% of colorectal cancer patients will develop metastases during follow-up.[35] This would be approximately 1900 colorectal patients in the total Dutch colorectal cancer population, and half of these patients would have metastases limited to the liver, which should be approximately 950 patients. Of these annual 2,600 patients with liver only disease (950 metachronous and 1,650 synchronous), approximately 20% (498 patients with CRLM) underwent liver resection in 2010, according to the results of the present study. Although not all patients who develop liver only metastases will have resectable liver metastases, the number of patients with CRLM who underwent liver resection in the Netherlands seems low. This is comparable to data from Morris et al.[21] and Manfredi et al.[22], who reported similar data. A recent study from the Eindhoven Cancer Registry in the Netherlands reported all patients with stage IV colorectal cancer and demonstrated that from 2004 to 2012 the number of patients who underwent liver surgery increased from 4% to 24%.[36]

This percentage may be a result of the decision-making process in management of patients with liver metastases. In the Netherlands, approximately 25 hospitals are performing liver surgery, but colorectal surgery is performed in almost all hospitals (>85). When patients are diagnosed in these hospitals, they are discussed in multidisciplinary teams, but specialist liver surgeons are not always involved in these meetings. Also the presence of a dedicated medical oncologist is demonstrated to be important in considering patients with CRLM suitable for neo-adjuvant chemotherapy.[37] Jones et al. demonstrated that even in a high-volume center (UK cancer network), almost two-thirds of patients with tumours deemed unresectable by non-liver surgeons, were considered potentially resectable by a panel of specialist liver surgeons.[38]

On the other hand, there is also considerable inter-individual variation in the decision-making process between liver surgeons.[39] This highlights the heterogeneity of oncological liver surgery and emphasises the importance of multidisciplinary liver tumour boards, to optimise the timing of surgical intervention and systemic treatment.

Although approximately 20% of the patients with CRLM undergo resection, non-CRLM patients are only considered to be candidates for liver resection in highly selected cases.[10, 12] The prevailing opinion that liver resection should not be considered as a curative option in non-CRLM patients may be insufficient, because 5-year disease-free survival after liver resection has been reported.[10,12,40] One of the reasons that non-CRLM patients might not be considered eligible for surgery is the fact that metastases are often diagnosed in an advanced disease stage, because imaging of the liver is not part of routine follow up for many malignancies. Another reason may be that patients with non-CRLM are often not exposed

to liver surgeons. With the emergence of multidisciplinary tumour boards it may be assumed that surgeons take part in the decision-making process concerning the treatment of non-CRLM patients more often than in the past, when this group of patients was mainly treated by medical oncologists.

Centralisation of complex upper gastrointestinal surgery, especially liver surgery and the effect on outcome have been reported.[41]. Centralisation of liver surgery in the Netherlands led to more 'high volume' and less 'low volume' and 'sporadic centers', as observed in the current study. Although it may be assumed that centralisation of liver resections may have led to improved short- and long-term outcome, this could not be drawn from the present study, because follow-up data are lacking.

In conclusion, the number of liver resections performed for metastatic disease increased over the past decade. Indications for liver resection seem to be expanding, reflected by the increasing percentage of elderly patients and the increasing amount of liver resections for multiple metastases. However, still only a minority of patients with liver metastases undergo a liver resection. Therefore we recommend that all patients with liver metastases (colorectal and non-colorectal liver metastases) should be discussed in a multidisciplinary tumour board, including an expert liver surgeon, in order to offer best possible treatment.

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CHAPTER 4

Resection of liver metastases in patients with breast cancer: survival and prognostic factors

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Abstract

Aims: Patients with breast cancer metastasized to the liver have a median survival of 4-33 months and treatment options are usually restricted to palliative systemic therapy. The aim of this observational study was to evaluate the effectiveness and safety of resection of liver metastases from breast cancer and to identify prognostic factors for overall survival.

Methods: Patients were identified using the national registry of histo- and cytopathology in the Netherlands (PALGA). Included were all patients who underwent resection of liver metastases from breast cancer in 11 hospitals in the Netherlands in the last 20 years. Study data were retrospectively collected from patient files.

Results: A total of 32 female patients were identified. Intra- and post-operative complications occurred in 3 and 11 patients, respectively. There was no post-operative mortality. After a median follow up period of 26 months (range: 0-188), 5-year and median overall survival after partial liver resection was 37% and 55 months, respectively. The 5-year disease-free survival was 19% with a median time to recurrence of 11 months. Solitary metastasis was the only independent significant prognostic factor at multivariate analysis.

Conclusion: Resection of liver metastases from breast cancer is safe and might provide a survival benefit in a selected group of patients. Especially in patients with solitary metastasis, the option of surgery in the multimodality management of patients with disseminated breast cancer should be considered.

Introduction

In the management of metastatic disease, resection of liver metastases has been performed more frequently in the last decade. Partial liver resection in patients with colorectal and neuroendocrine liver metastases has become widely accepted and is safe and effective. A 5-year overall survival of 20-50% has been reported, in comparison to only few patients surviving 5 years after systemic therapy for the liver metastases.[1-3] In contrast, patients with disseminated non-colorectal, non-neuroendocrine liver metastases are only referred for surgical resection in selected cases.

Liver metastases are present in 20-25% of the patients with stage IV breast cancer and are the initial sign of distant dissemination in 5% of the cases.[4] Historically, these patients have a poor prognosis with a median survival of 4-14 months when treated with standard chemotherapy regimens.[5, 6] More recent studies of patients treated with modern multimodality antihormonal- and chemotherapy, report a median survival of 24-33 months.[7, 8] In a nationwide cancer registry from the Netherlands patients with stage IV breast cancer diagnosed between 2003 and 2007 have a 5-year survival of 21% and a median survival of 24 months.

Metastatic breast cancer is a systemic disease and microscopic tumour deposits may exist in various sites of the body, though not always detected by standard and modern imaging techniques. As a result, partial liver resection has not often been proposed to metastatic breast cancer patients. Multimodality non-surgical treatment is generally considered as the most appropriate way to treat these patients, including chemotherapy, antihormonal therapy or directed targeted agents.[5, 9, 10]

However, partial liver resection in disseminated non-colorectal, non-neuroendocrine malignancies becomes more accepted, because of its additional effectiveness. With advances in surgical techniques, anesthesia management and post-operative patient care, morbidity and mortality are significantly reduced. Improved chemotherapy regimens allow a better control of metastatic disease and possibly reduce the number and/or diameter of liver metastases, which results in a favourable situation before resection.[10]

The reports of partial liver resection in patients with breast cancer are heterogenous. The results show a tendency to an improved long term outcome in selected patients, with 5-year overall survival ranging from 21 to 61% and median overall survival between 24 and 63 months.[10-23] However, there is no clear consensus on selection criteria for referring patients for surgical resection. Few independent prognostic factors for post-operative survival have been identified with a wide variation between the various reports.

In order to analyse a substantial cohort of patients with adequate follow up, we reviewed the outcome of patients after resection of breast cancer liver metastases in the Netherlands over the last 20 years. The aim of this study was to evaluate disease-free and overall and to identify prognostic factors for long-term survival.

Patients and methods

Patients and data

Patients were identified using the results of a research question in the PALGA database which is the nationwide network and registry of histo- and cytopathology in the Netherlands, that registers all pathologic reports since 1991.[24] All patients who underwent a resection of breast cancer liver metastases with potential feasibility to achieve a R0 resection were included. The hospitals were visited for retrospective collection of study data from the patient files. A data file was used, recording information of the primary tumour, liver metastases, surgery, post-operative stay, pathology and multiple other clinical factors.

Surgery

Localisation of the metastases was specified in liver segments, according to Couinaud's classification. Resection margins were defined as complete microscopic resection (R0), microscopic residual disease (R1) or macroscopic residual hepatic or extrahepatic disease (R2).

Outcome variables

Post-operative morbidity and mortality were defined as complications and death within the first 30 days after surgery. Disease-free survival (DFS) was defined as the interval between partial liver resection and recurrence of disease. In case of an incomplete resection or extrahepatic metastases at the time of liver surgery, disease-free survival was defined as 0 months. Overall survival (OS) was determined from the date of surgery until the date of last follow-up or death. Death was unspecified by cause, as it was in some cases impossible to require essential information because of the ethical guidelines by the central committee of research involving human subjects.

Statistical considerations

Survival outcomes were calculated by Kaplan Meier survival analysis. Prognostic factors for long-term survival were identified by univariate survival analysis, according to Cox proportional hazards regression methodology. Factors with a p-value of <0.05 in univariate analysis were included in multivariate analysis. Statistical significance with a p-value of less than 0.05 was considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

Clinical characteristics

Using the PALGA registry, all 32 female patients were identified who underwent resection of liver metastases from breast cancer with curative intent over the last 20 years in the Netherlands. Surgery was performed in 11 different hospitals from January 1994 to September 2010. Median age was 50 years (range: 31-67).

Primary breast tumour, treatment and histological diagnosis

All patients were operated for primary breast tumour with either breast conservative treatment or mastectomy. Twenty patients had invasive ductal carcinoma, 4 patients had lobular carcinoma and one patient had mixed ductal and lobular carcinoma. In one patient only ductal carcinoma in situ was found in the original specimen, suggesting the invasive component was missed or an occult breast cancer was present in the contralateral breast. In 6 patients, the primary tumour was only specified as 'breast cancer'. In 25 patients, immunohistochemical data of the hormone receptor status of the primary tumour was available, reporting 11 ER+ PR+ tumours, 9 ER+ PR- tumours and 5 ER- PR- tumours. In 11 patients, data was available on Her2 overexpression, which was demonstrated to be positive in 8 patients.

Locoregional metastases

At initial presentation 23 patients had regional lymph node metastases and underwent an axillary dissection. Three patients developed axillary metastases during follow up at 9, 13 and 18 months, respectively. Two patients developed a local recurrence at 36 and 109 months, respectively. In 4 patients there was no evidence of locoregional metastatic disease or local recurrence. Adjuvant radiotherapy was given in 22 patients, 19 patients were treated with adjuvant chemotherapy, 17 patients with antihormonal therapy and 4 patients with trastuzumab. Most patients received a combination of several adjuvant therapies.

Preoperative evaluation

Diagnosis of the liver metastases was based on ultrasound, CT-, MRI- or PET-scanning or a combination. Preoperative histological examination by needle biopsy was performed in 19 patients. In 2 patients the biopsy was inconclusive, but liver surgery was performed because of high probability of malignancy on imaging. Median interval between treatment of the primary tumour and histological diagnosis of liver metastases was 33 months (range: 0-219). The presentation of liver metastases, based on histological diagnosis, was synchronous (within 6 months) in 6 patients and metachronous (after 6 months) in 26 patients. A solitary metastasis was identified in 22 patients. Median diameter of the largest metastasis was 2.5 cm (range: 0.7 to 9 cm). Liver metastases were localised in one lobe in all but one patient.

Preoperative evaluation of extrahepatic metastases
The presence of extrahepatic dissemination was evaluated by chest X-ray or CT-scan only in 11 patients, PET-scan only in 1 patient, or a combination in 19 patients. Extrahepatic metastases were present during liver surgery in 5 patients (i.e. bone metastases in 3 patients, cervical lymph node in 1 patient and colon metastases in 1 patient).

Neo-adjuvant therapy
Prior to liver resection, 13 patients received neo-adjuvant chemotherapy, 5 patients received antihormonal therapy and 2 patients received trastuzumab and bevacizumab, respectively.

Surgical procedure
A right subcostal incision was performed in most patients, allowing assessment of intra-abdominal spread of disease, which would be a contraindication for liver resection. In one patient previously undiagnosed extensive intraabdominal disease was found. This patient did not undergo resection and was excluded from this study. In 32 of the 33 patients, intra-abdominal spread of disease was absent, and partial liver resection performed. In 21 patients intraoperative ultrasound was performed. Major resection (3 segments or more) was performed in 13 patients, minor resection (less than 3 segments) in 19 patients. Liver resection was combined with radiofrequent ablation (RFA) in 2 patients. Pringle maneuver was performed in 12 patients with a median time of 25 minutes (range: 10-50). In 2 patients an iatrogenic lesion of the spleen occurred, which required splenectomy. In 1 patient an iatrogenic lesion of the left hepatic duct occurred, which required post-operative endoscopic retrograde cholangiographic (ERC) stenting of the duct. A radical (R0) resection was performed in 29 patients whereas microscopically positive margins (R1) were present in 3 patients. Of the 5 patients with extrahepatic disease, 3 were treated with curative intent for their extrahepatic metastases. The patients with the colonic metastasis and neck lymph node metastasis underwent a hemicolectomy and a modified neck dissection, respectively. One patient with a bone metastasis in the sternum received radiation therapy with curative intent.

Post-operative course
Post-operative complications occurred in 11 patients and treated conservatively in 4 patients (ileus *n*=1, pneumonia *n*=1, pleural effusion *n*=2). One patient with pleural effusion, two patients with a lesion of the sinus pleurae and one patient with an intra-abdominal abscess needed percutaneous drainage. One patient developed stenosis of the bile duct and another patient had bile leakage post-operatively. Both were treated with ERC drainage of the bile duct. In one patient who also underwent a hemicolectomy, anastomotic leakage and wound infection occurred, which were treated with reoperations and end colostomy. There was no

post-operative mortality. Median post-operative length of stay was 7 days (range: 4-58 days). Adjuvant systemic chemotherapy was given in 14 patients.

Disease-free survival

Median follow-up of the entire cohort after liver resection was 26 months (range: 0-188 months). The 5-year disease-free survival was 19% with a median time to recurrence of 11 months. Four patients were classified as having no disease-free survival: 2 patients because of a non-radical resection (R1), 1 patient had non-treated extrahepatic disease at the time of liver resection, and 1 patient had both. Nineteen patients developed recurrences after liver surgery, of which 9 experienced new liver metastases, 5 had extrahepatic metastases, 3 had both and 2 unknown localisations. At the date of this analysis, 8 patients had no evidence of disease with a median follow-up of 27 months (range: 0-188).

Overall survival

The 5-year overall survival from the date of liver resection was 37% with a median survival of 55 months. Three patients were alive 5 years after liver surgery, including one patient with 15 years follow-up without evidence of recurrent disease. The group of 3 patients with an R1 resection had a median survival of 60 months and a 5-year overall survival of 33%.

Prognostic factors

Prognostic factors of overall survival were analysed and reported in Table 1. Significant factors for long-term survival in univariate analysis were estrogen positive receptor status of the primary tumour, solitary metastasis and unilobar distribution of the metastases. Solitary metastasis was the only independent prognostic factor in multivariate analysis. Patients who underwent resection of a solitary liver metastasis had a 5 years overall survival of 68% (Figure 1). This difference in the number of metastases was also significant when the limit was set on 3 metastases. Median and 5-year disease-free survival in the group of patients with solitary metastasis were 11 months and 22% respectively, versus 5 months and 0% in the group of patients with multiple metastases. This difference was not significantly different.

Table 1. Prognostic factors for overall survival in patients after resection of liver metastases from breast cancer

Factor	*n*	Median OS (months)	5-year OS (%)	Univariate *p*-value	Multivariate *p*-value
Age					
<50years	16	60	38		
≥50 years	16	55	37	0.283	
Histology primary tumour					
Invasive ductal carcinoma	20	60	42		
Invasive lobular carcinoma	4	27	38 (at 44 months)	0.319	
Hormone receptor status primary					
Estrogen +	20	60	49		
Estrogen -	5	12	25 (at 44 months)	**0.008****	0.070
Her2 overexpression					
Present	8	60	31		
Absent	3	No events	No events	0.370	
Needle biopsy					
Not performed	13	47	0 (at 47 months)		
Performed	19	60	46	0.279	
Interval between diagnosis of the primary tumour and liver metastases					
Synchronous	6	103	53		
Metachronous	26	47	32	0.254	
Number of metastases					
Solitary	22	103	68		
Multiple	10	47	0	**0.018****	**0.047****
Number of metastases					
≤3 metastases	28	55	48		
>3 metastases	4	12	0	**0.016****	
Size					
<5cm	27	55	34		
≤5cm	5	27	50	0.870	
Distribution					
Unilobar	31	55	38		
Bilobar	1	12	0 (at 12 months)	**0.005****	0.754
Extrahepatic metastases					
Absent	26	60	46		
Present	5	34	0	0.074	
Neo-adjuvant chemotherapy					
Yes	13	60	39		
No	19	55	36	0.948	
Type resection					
<3 segments	19	47	42		
≥3 segments	13	55	24	0.910	
Resection margins					
R0	29	55	40		
R1	3	60	33	0.887	
Adjuvant Tx					
Yes	12	47	33		
No	18	55	31	0.786	

OS: overall survival; Tx: therapy.** In bold: statistically significant with $p<0.05$

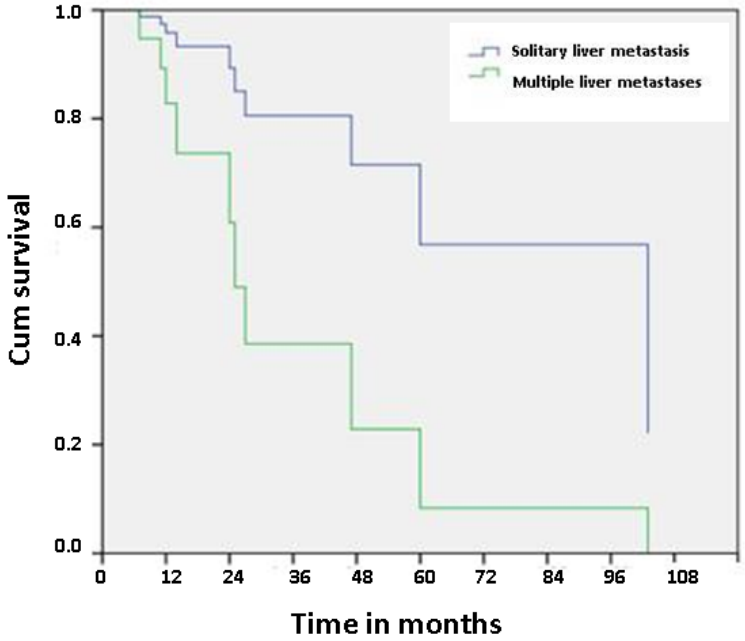

Figure 1. Overall survival in patients after resection of solitary versus multiple liver metastases from breast cancer (p<0.05).

Discussion

In the present study the 5-year overall survival after resection of liver metastases in patients with breast cancer was 37% with a median survival of 55 months. The survival data in the literature of patients with liver or visceral metastases from breast cancer receiving systemic therapy show a median survival of 4-33 months.[4, 7, 8] Compared with these data, liver resection in selected patients might provide a relevant survival benefit. The survival outcomes of the present study are comparable with previously published reports (Table 2).[10-19, 21-23] Median overall survival in the literature ranges between 24 and 63 months and 5-year overall survival between 21% and 61%.

In the present study a post-operative mortality rate of 0% and post-operative complication rates of 34% are described, respectively. In general, treatment of liver metastases aims to minimize intraoperative and post-operative morbidity.[10] This morbidity is often one of the reasons to reject resection as a treatment option. Although in this study minor complications occurred relatively frequent, most patients recovered completely. This relatively high complication rate might be a reflection of an independent registration of the results by an external reviewer, but also because of the relatively low number of patients treated in each center. Although post-operative mortality did not occur in these series, centralisation of liver

surgery might possibly decrease the number of complications in future studies. Initiatives to further centralise and register patients in a nationwide database are now conducted in several countries including the Netherlands, in order to improve outcome.

Table 2. Review of reports describing the outcome in patients with metastatic breast cancer to the liver, treated with liver resection.

Author	Year	*n*	Post-operative morbidity (%)	Post-operative mortality (%)	5-year OS (%)	Median OS (months)
Selzner[18]	2000	17	0	6	22	24
Yoshimoto[23]	2000	25	-	0	27	34
Elias[12]	2003	54	12.9	0	34	34
Vlastos[21]	2004	31	-	0	61	63
Ercolani[13]	2005	21	20.5	0	25	40
Sakamoto[17]	2005	34	-	0	21	36
Weitz[22]	2005	29	-	-	-	48
Adam[10]	2006	85	26	0	37	32
Martinez[16]	2006	20	-	-	33	32
Caralt[11]	2008	12	16.6	0	33	36
Lubrano[15]	2008	16	37.5	0	33	42
Thelen[19]	2008	39	13	0	42	-
Hoffman[14]	2010	41	21	0	48	58
Present series	2011	32	44	0	37	55

OS: overall survival

Significant prognostic factors of overall survival in univariate analysis were estrogen positive receptor status of the primary tumour, solitary metastasis and unilobar distribution of the metastases. Solitary metastasis was the only independent prognostic factor at multivariate analysis. Compared with previous reports (Table 3), prognostic factors differ in the various studies. This could possibly be explained by the small number and the diverse clinical characteristics of the patients. Similar as in the present study, positive estrogen receptor status was a significant factor for long-term survival in two other studies. Interestingly, in one report a negative status was a significant prognostic factor. Prognostic significance of a low number of metastases was confirmed by two other reports. According to the different levels of significance reported, the various factors are no absolute criteria to in- or exclude patients for liver surgery, but can be taken into account in providing optimal treatment for individual patients.

Response to preoperative chemotherapy was an important factor in patient selection for surgery by Adam et al. (Table 3).[10] Several studies recommend neo-adjuvant chemotherapy for patients planned for partial liver resection.[10, 12] In the present study only a proportion of

patients were treated with neo-adjuvant systemic therapy. Analysing this factor, regardless of the degree of response, treatment with neo-adjuvant systemic therapy showed no significant difference in survival outcome. However, in unresectable tumours, it might be worth considering chemotherapy to downsize the metastatic lesion to facilitate complete resection. In addition, neo-adjuvant or adjuvant chemotherapy may treat potential micro-metastases. On the other hand, care should be taken with neo-adjuvant chemotherapy making well-responsive metastases difficult to locate for surgery. Chemotherapy also puts enormous strain on the liver parenchyma which potentially compromises the quality of residual liver after resection. Therefore, discussing patients with liver metastases in a multidisciplinary team before starting with chemotherapy is essential.

The results of this study are the first nationwide data available in the Netherlands, including all patients treated surgically for liver metastases from breast cancer over the last 20 years. According to the Dutch Cancer Registry the total incidence of invasive breast cancer in the previous 10 years was 10,000 – 13,000 patients each year. Of them, approximately 20-30% will develop disseminated disease. Thus, in the last 20 years in the Netherlands only a very small portion of the patients with stage IV breast cancer underwent surgery of liver metastases with curative intent.

Although this study contains a low number of patients, as most similar studies, it confirms previous results and provides additional data. Especially the results of surgery in patients with solitary metastasis are promising with a 5-year overall survival of more than 50%. A limitation of this study, however, is the possibility of bias in selecting patients with favourable prognostic features for liver resection. It cannot be concluded whether the prolonged survival is the effect of the liver resection itself or the favourable biology of the highly selected patients.

In two patients radiofrequent ablation (RFA) was performed. Limited data is reported in the literature on the treatment of liver metastases of breast cancer with RFA. For colorectal liver metastases several studies have been performed, concluding that survival rates are similar between surgery and RFA for tumours less than 3 cm.[25, 26] Prospective studies with long-term follow-up are lacking to compare resection and RFA with respect to recurrence, disease-free survival and overall survival rates. Data of RFA in breast cancer liver metastases are limited to small retrospective series that have demonstrated an improvement in survival with adjuvant RFA compared to chemotherapy alone. [27] Until new data will become available, surgery remains the option of choice to completely remove the metastatic lesions in resectable metastatic breast cancer confined to the liver.

Table 3. Prognostic factors for overall survival in patients after resection of liver metastases from breast cancer. Overview of relevant reports.

	Age	ER-status	Her2 overexpression	Previous extrahepatic metastases	Time from primary to metastases	Number of metastases	Distribution	Response to pre-operative Ctx	Extent of resection	Resection margins
Adam[10]	-	-	-	-	-	-	-	MV *p*=0.008 (good response)	-	MV *p*=0.0001 (R0)
Elias[12]	-	MV *p*=0.03 (+)	-	-	-	-	-	-	-	-
Hoffman[14]	-	-	-	-	MV *p*=0.0097 (>12 months)	-	-	-	-	MV *p*=0.0015 (R0)
Lubrano[15]	UV *p*=0.006 (>50 y)	UV *p*=0.018 (-)	-	-	-	MV *p*=0.04 (solitary)	-	-	MV *p*=0.01 (minor)	-
Martinez[16]	UV *p*=0.02 (>50y)	UV *p*=0.02 (+)	UV *p*=0.02 (+)	-	-	UV *p*=0.002 (≤2)	-	-	-	-
Sakamoto[17]	-	-	-	MV *p*=0.027 (absent)	-	-	-	-	-	-
Thelen[19]	-	-	-	UV *p*=0.01 (absent)	-	-	-	-	-	MV *p*=0.01 (R0)
Present serie	-	UV *p*=0.008 (+)	-	-	-	MV *p*=0.047 (solitary)	UV *p*=0.05 (unilobar)	-	-	-

ER: estrogen resecptor, Ctx: chemotherapy, UV: univariate analysis; MV: multivariate analysis; +: positive; - : negative; between brackets: longer survival in case of.

Conclusion

Resection of liver metastases from breast cancer is safe and might provide a survival benefit in a selected group of patients. The option of partial liver resection in the multimodality management in patients with liver disseminated breast cancer, especially in case of solitary metastasis, should be considered. Various clinical factors are not absolute contraindications for resection, but can be helpful in decision making for resection in individual cases.

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CHAPTER 5

Hepatic resection for metastatic melanoma in the Netherlands: survival and prognostic factors

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Abstract

Aims: Patients with liver metastases of melanoma have a very poor prognosis, with a median overall survival of less than 6 months. There are several small heterogeneous studies that have shown an association with prolonged survival in those patients treated with liver resection, but the role of surgery remains unclear. We evaluated the safety and efficacy of liver resection in a population-based study in the Netherlands for patients with metastatic melanoma and assessed factors that could affect disease-free and overall survival.

Methods: Patients with liver metastases from melanoma who underwent potentially curative resection were identified between 1994 until 2010 using the PALGA-database; a nationwide network and registry of histo- and cytopathology in the Netherlands. They were retrospectively evaluated for clinical and pathological factors with respect to recurrence and survival using Kaplan Meier curves to assess survival and univariate regression analyses for assessing potential prognostic factors.

Results: A total of 32 patients were identified in 15 hospitals; 19 men and 13 women. The median age of the patients at the time of liver resection was 52 years (range: 27-69 years). Post-operative complications occurred in 5 patients (15%), without post-operative mortality. The median follow-up was 21 months (range: 3-65 months). The median disease-free survival was 11 months (range: 0-57 months) and the median overall survival was 29 months (range: 4-66 months). Significant prognostic factors for overall survival in univariate analysis were the distribution and number of metastases, as well as the type of liver resection (major or minor).

Conclusion: Liver resection in patients with resectable metastatic melanoma is safe and might be associated with a prolonged survival in a highly selected group of patients.

Introduction

Depending on the clinical and pathological characteristics of the primary tumour, up to one third of patients with melanoma develop distant metastases.[1-3] A common site for distant metastases is the liver. Especially patients with ocular melanoma may have liver metastases present at the time of diagnosis, in 40% of the cases, and the liver becomes involved in 95% of patients who develop metastatic disease.[4] Cutaneous melanoma also metastasises to the liver in 15% to 20% of the patients who develop metastatic disease and, on autopsy liver involvement is demonstrated in 55-75% of patients.[3,5]

Patients with liver metastases have a very poor prognosis, with a median survival of approximately 4 months and a 5-year survival of less than 5%.[6] Response rates on traditional DTIC-based chemotherapy regimens are often low, with percentages below 10%.[7] Recent treatment with BRAF inhibitors or anti-CTLA4 has yielded response rates with a significant improvement in 1-year survival, but long-term survival benefits are to be awaited.[8,9] Moreover, these new agents may induce complications, with considerable morbidity and development of other skin cancers. The optimal treatment strategy for patients with isolated liver metastases from melanoma remains unclear, even with these new treatment options.

In patients with colorectal liver metastases, liver resection is widely accepted as proven effective with 5-year survival of 20-50%.[10-12] With improvements in surgical techniques and anesthetic management, the perioperative mortality and morbidity have decreased, which makes partial liver resections relatively safe. However, patients with disseminated malignancies of non-colorectal, non-neuroendocrine origin to the liver are only referred for surgical therapy in selected cases.

The objective of this study was to evaluate all patients in the Netherlands in the past 20 years with metastatic melanoma of the liver who were treated with liver resection for safety, survival and to identify potential prognostic factors to predict long-term survival after resection.

Patients and methods

Patients and data collection

Patients were identified by the results of a nation-wide research question in the PALGA-database; a nationwide network and registry of histo- and cytopathology in the Netherlands, which registers all pathologic reports since 1991.[13] All patients who underwent a potentially curative liver resection for metastatic melanoma between 1994 until 2010 were included. Hospitals were visited to collect retrospective data from the patient files. The following data were collected for each patient from the file: demographics, anatomical location and

histological characteristics of the primary melanoma, details of the primary treatment of the melanoma, time interval from initial treatment of the melanoma to metastasis, surgical procedures, number, location and size of the liver metastases, recurrence, death date, mortality and morbidity.

Outcome variables

Post-operative mortality and morbidity included all deaths or complications attributed to liver resection and all deaths or complications within 60 days of the operative procedure. Disease-free survival was defined as the time from liver resection until disease recurrence. In some patients, resection was not complete and disease-free survival was defined as 0 months. Overall survival was defined as the time between liver resection until the date of last follow up or death. Death was not specified by cause, because it was not possible to detect this because of the ethical guidelines of using de-identified data.

Statistical analyses

All statistical analyses were carried out using the Statistical Package for the Social Sciences version 16.0 (SPSS, Inc., Chicago, Illinois, USA). Survival outcomes were calculated using Kaplan-Meier survival curves. Prognostic factors for long-term survival were identified by univariate analysis according to Cox proportional hazard regression methodology. Because of the small number of patients, multivariate analysis was not performed. We considered a *p*-value of less than 0.05 significant.

Results

Patient and tumour characteristics

A total of 49 patients were identified in 15 hospitals using the PALGA database; eight patients underwent only a diagnostic liver biopsy only, two patients underwent an isolated liver perfusion and seven patients were found to have unresectable disease per-operatively. A total of 32 patients who underwent liver resection between 1994 and 2010 were evaluated in the present study. The median follow up was 21 months (range: 3-65 months). The median age during liver resection was 52 years (range: 27-69 years). There were 19 men and 13 women. The median interval between resection of the primary tumour and liver resection was 62 months (range: 15-188 months). The origin of the primary tumour was ocular melanoma in 12 patients and cutaneous melanoma in 16 patients; in four patients, the primary location of the tumour was unknown. The median Breslow thickness of the primary tumour was 2.0mm (range: 0.5 – 11.0mm). Before liver resection, 13 patients were treated with a therapeutic lymph node dissection for regional metastatic disease (inguinal lymph node dissection *n*=5,

axillary lymph node dissection *n*=10, cervical lymph node dissection *n*=1). In 16 patients liver metastases were the first and only site of metastases.

Surgery characteristics

The number of metastases ranged from 1-10; 18 of the patients (52%) had a solitary liver metastasis. The distribution of the metastases was unilobar in 23 patients and bilobar in nine patients. The median size of the largest metastasis was 24 mm (range: 10-160 mm). Patients were treated with a hemihepatectomy (*n*=9), extended hemihepatectomy (*n*=2), segmentectomy (*n*=11) or with a non-anatomical resection (*n*=10). Resection was radical (R0) in 23 patients, microscopically irradical (R1) in six patients, macroscopically irradical (R2) in one patient and unknown in two patients.

Post-operative mortality was not observed. Post-operative complications occurred in five patients (15%). Four patients developed liver failure, ileus, pneumonia or pleural effusion. All of these complications resolved with conservative treatment. One patient developed an intra-abdominal infected hematoma, which required percutaneous drainage and antibiotic treatment. The seven patients who underwent explorative laparotomy and were found to have unresectable disease did not experience post-operative morbidity.

Overall survival and disease-free survival

The median disease-free survival was 11 months (range: 0-57 months) and the median overall survival was 29 months (range: 4-64 months) (Figure 1a and b). There was one patient with a survival of more than 5 years, and 5-year overall survival was 3%.

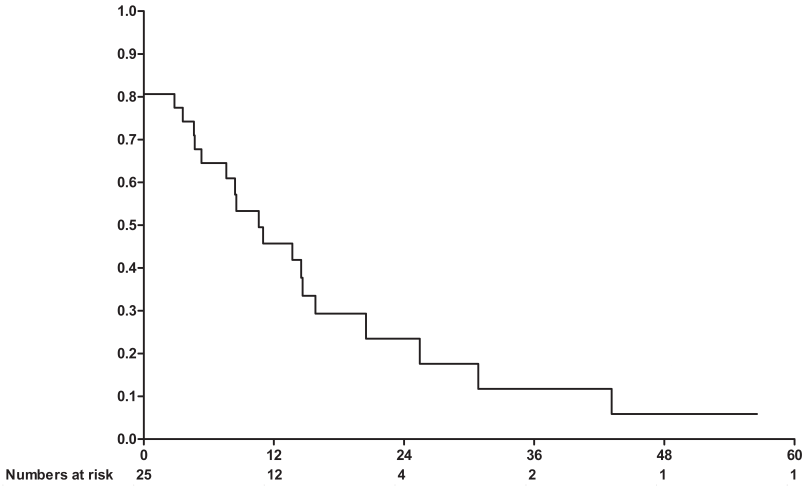

Figure 1A. Disease-free survival of patients who underwent liver resection for metastatic melanoma in months. Median disease-free survival: 11 months.

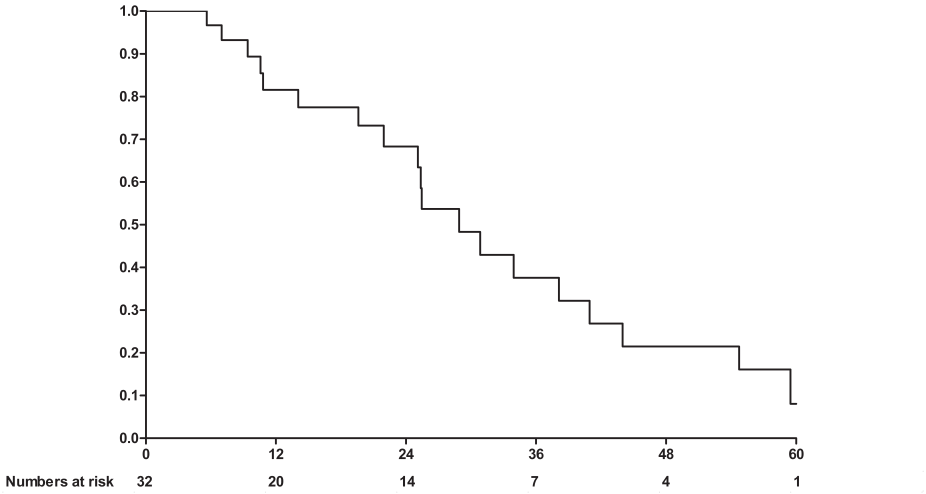

Figure 1B. Overall survival of patients who underwent liver resection for metastatic melanoma in months. Median overall survival 29 months.

Prognostic factors

Significant factors for prolonged disease-free survival in univariate analysis were the number of liver metastases and a cutaneous location of the primary melanoma (Table 1). Significant factors associated with prolonged overall survival in univariate analysis were the number (p= 0.023) and the distribution of liver metastases (p= 0.002), as well as a minor resection (p= 0.021) (Figure 2a-c). There was a trend towards prolonged survival in male versus female patients (p= 0.054).

Table 1. Potential prognostic factors in univariate analysis for disease-free survival and overall survival after liver resection in patients with metastatic melanoma in the Netherlands from 1994-2010

Factors	*n*	Median DFS (months)	*p*-value	Median OS (months)	*p*-value
Sex			0.153		0.054
Male	19	14		38	
Female	13	8		25	
Primary tumour			**0.033****		0.996
Cutaneous	16	15		25	
Ocular	12	8		34	
Unknown	4	9		29	
Breslow's dept			0.875		0.623
<2mm	8	8		22	
≥2mm	7	15		25	
Number metastases			**0.030****		**0.023****
Solitary	18	14		38	
≥2	13	8		25	
Distribution			0.301		**0.002****
Unilobar	23	14		38	
Bilobar	9	8		22	
Resection			0.687		**0.021****
≤3 segments	13	13		38	
>3 segments	19	7		22	
Resection margins			**0.000****		0.905
R0	23	15		25	
R1/R2	7	0		29	
Age at time of liver resection			0.715		0.623
<60 years	25	10		31	
≥60 years	7	4		25	
Size metastasis			0.279		0.453
<50 mm	27	8		29	
≥50 mm	5	2		11	

DFS: disease-free survival; OS: overall survival; **Bold indicates $p<0.05$

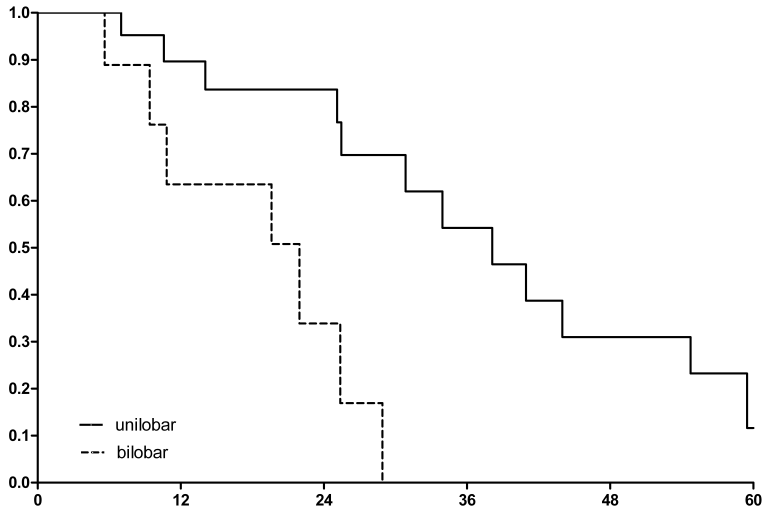

Figure 2A. Overall survival (OS) in months after liver resection for metastatice melanoma in patients with an unilobar (*n*=23; median OS 38 months) or a bilobar distribution (*n*=9; median OS 22 months) (*p*=0.002).

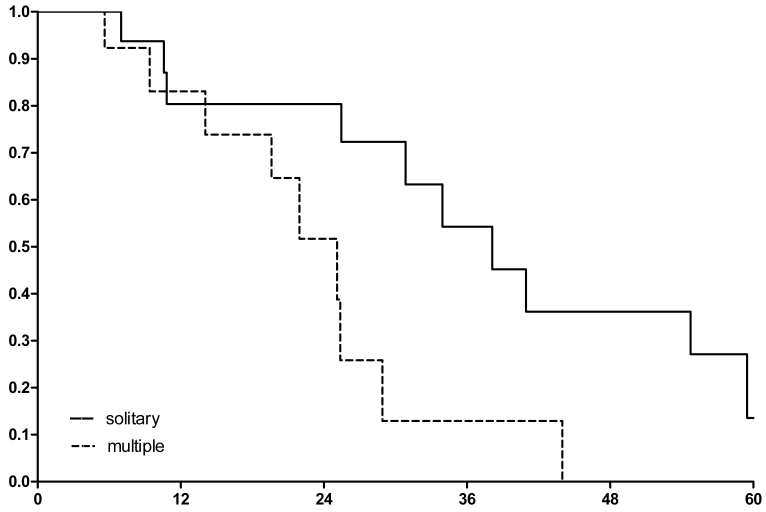

Figure 2B. Overall survival (OS) in months after liver resection for metastatic melanoma in patients with solitary (*n*=18; median OS 38 months) or multiple liver metastases (*n*=13; median OS 25 months) (*p*=0.023).

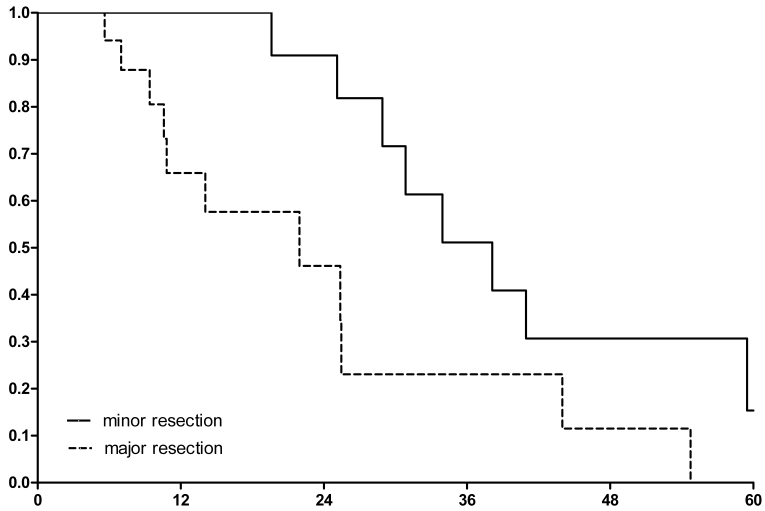

Figure 2C. Overall survival (OS) in months after minor liver resection, which includes less than 3 liver segments (*n*=13; median OS 38 months) or major liver resection, which includes three or more liver segments (*n*=19; OS 22 months) for metastatic melanoma (*p*=0.021).

Discussion

This study describes the first nationwide series of melanoma patients in the Netherlands treated surgically for liver metastases in the last 20 years. A histological diagnosis was available in 49 patients and only 32 (65%) patients underwent a potentially curative surgical resection. The median overall survival in this small and highly selective group of patients was 29 months. In univariate analysis, patients with solitary metastasis, unilobar disease, or a minor resection (less than 3 segments) had a significantly improved overall survival. Although this study contains a low number of patients it confirms results from previous studies in the literature and provides additional data.

In the literature, metastatic melanoma patients receiving systemic treatment without surgical treatment have a median survival of less than 6 months.[6] Several surgical studies have shown an association between liver resection in melanoma patients and improved survival in patients with stage IV disease.[14-38] Adam et al. reported a large series of patients with metastatic melanoma who underwent liver resection; they found a median disease-free and overall survival rate of 11 and 35 months, respectively.[23] Pawlik et al. also reported a series of 40 patients who underwent liver resection for metastatic melanoma. They found a median disease-free and overall survival of 8 and 28 months, respectively.[25] Multiple other studies reported similar overall survival (Table 2).

Data from the present study support the results found in previous studies, although 5-year overall survival was only 3% in the present study, whereas in other studies, these percentages range between 36% and 10%.[23,25] This may partly be explained by the short median follow-up time of 21 months. The 3-year-overall survival and 4-year-overall survival rates are 22%, respectively, 12.5% which are more in agreement with data found in the literature. Several investigators have attempted to identify criteria to make the decision for liver resection in metastatic liver disease. For colorectal liver metastases Fong et al. have made specific recommendations on the basis of the number and size of metastases, disease-free interval from primary to metastases, presence of lymph node positivity, and pre-operative carcinoembryonic antigen levels.[39] There are fewer reports on the selection of patients for liver resection in non-colorectal, non-neuroendocrine metastases and even less reports specifically for metastatic melanoma.

Table 2. Review of reports describing factors associated with improved survival in patients with metastatic melanoma who underwent liver resection.

Reference	Year	*n*	OS in months	DFS in months	Prognostic factors
Adam et al.[23]	2006	148	35	11	Age ≤60 DFI≥12 months No extra-hepatic disease R0/1-resection Minor liver resection**
Pawlik et al.[25]	2006	40	28	8.3	Unilobar distribution Neo-adjuvant chemotherapy Size ≤5cm Metachronous metastases Solitary metastasis*
Frenkel et al.[24]	2009	35	15-55	35-37	R0-resection ≤6 metastases*
Rose et al.[21]	2001	24	28	12	R0-resection
O'Rourke et al.[18]	2007	20	42	18	R0-resection DFI ≥24 months**
Weitz et al.[20]	2005	17	42	17	Size ≤5cm No extrahepatic nodal disease**
Reddy et al.[37]	2007	11	44	13	DFI≥6 months Adjuvant chemoradiotherapy**
Herman et al.[36]	2006	10	22	NR	NR
Elias et al.[32]	1998	10	18	NR	NR
Present study	2011	32	29	11	Solitary metastasis Unilobar distribution Minor liver resection*

OS: overall survival; DFS: disease-free survival; DFI: Disease-free interval between detection of primary tumour and liver resection; NR not reported. *: Statistically significant ($p<0.05$) in univariate analysis; ** Statistically significant ($p<0.05$) in multivariate analysis

In previous studies, a number of different prognostic factors have been shown to be important for survival.[17,18,20,21,24,28-30,37] These differences could possibly be explained by the small number and the diverse clinical characteristics, particularly the origin of the primary tumour, in the patients reported. Pawlik and colleagues reported a significantly improved long-term survival in patients with primary cutaneous melanoma, with 5-year survival rates in this group of 20.5% versus no survivors in the patients with primary ocular melanoma. They did not find other clinico-pathological factors to be predictive for an improved long term survival.[25] Unlike the results of Adam et al. the size of the liver metastases was not a prognostic factor for long-term survival in the present study.[23] This might be explained by the fact that only five patients with a diameter of more than 5 cm were identified and 27 had a diameter of less than 5cm. R0 resection was also not a significant predictive factor for long-term survival. According to the different levels of significance reported, the various factors are no absolute reasons to include or exclude patients for liver resection, but can be taken into account in providing optimal treatment for individual patients.

In the present study there was no mortality, but five of the 32 patients (15%) experienced post-operative complications. This complication rate might be a reflection of an independent registration of the results by an external reviewer, but may also relate to the relatively low number of patients treated in each center. Mortality did not occur in this series, but centralisation of liver surgery might possibly decrease the number of complications in the future. Initiatives to further centralise and register patients in a nationwide database are now being conducted in several countries including the Netherlands.

Especially in melanoma patients, immunological treatment modalities have been studied intensively, with promising results.[8,40,41] Recent reports show an improved survival in patients treated with ipilimumab or activated, mutated BRAF inhibitors.[42] The role of surgery in patients with stage IV who become resectable after treatment with these new agents has to be established. Besides systemic treatment, other modalities such as isolated liver perfusion have been explored in patients with melanoma metastases in the liver. Various reports show survival benefit in patients treated with melphalan or TNF, but these treatments are still experimental and survival benefit is limited, with a median survival of approximately 10 months.[43-45] The ideal therapeutic approach for melanoma patients with limited liver metastases is unclear; however, complete metastasectomy must be considered as a treatment option in highly selected patients.[46]

Conclusion

Liver resection is safe in resectable metastatic melanoma and might be associated with a prolonged survival in highly selected patients.

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CHAPTER 6

Management of liver metastases in colorectal cancer patients: a case-control study of systemic therapy versus liver resection

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Abstract

Objective: To evaluate and compare the overall survival (OS) in case-matched patient-groups treated either with systemic therapy or surgery for colorectal liver metastases (CRLM).

Methods: Patients with CRLM, without extra-hepatic disease, treated with chemotherapy with or without targeted therapy in two phase III studies (*n*=480) were selected and case-matched to patients who underwent liver resection (*n*=632). Matching criteria were sex, age, established prognostic factors for survival (clinical risk score). Available computed tomography (CT)-scans of patients treated with systemic therapies were reviewed by three independent liver surgeons for resectability. Survival was compared between patients with resectable CRLM (based on CT-scan review) who were treated with systemic therapy versus patients who underwent liver resection.

Results: A total of 96 patients treated with systemic therapy were included. Pre-treatment CT-scans of the liver were available for review in 56 of the systemically treated patients, and metastases were unanimously considered resectable in 36 patients (64.3%) (complex resectable: *n*=25; 69%). These 36 patients were case matched with 36 patients who underwent liver resection (wedge resection or segmentectomy: *n*=26; 72%). Median OS in the patient group treated with systemic therapy was 26.5 months (range: 0-81 months), which was significantly lower than in case-matched patients who underwent liver resection (median OS 56 months; range: 6-116) (*p*=0.027).

Conclusions: In this case-matched control study, surgery provided superior OS rates compared to systemic therapy for CRLM. Resection of CRLM should always be considered, preferably in a dedicated liver centre, since not all patients that qualify for resection are identified as such.

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-death worldwide.[1] CRC patients develop metastases in 30-40%, depending on various factors such as T-stage, N-stage or histological subtype of the CRC (i.e. mucinous, signet ring cell or adenocarcinoma).[2] Approximately 20% of patients present with synchronous distant metastases (stage IV disease) and another 20% will develop metachronous metastases, predominantly located in the liver.[3-4]

In terms of treatment, liver resection is considered the standard of care in patients with resectable colorectal liver metastases (CRLM), with 5-year survival rates ranging from 35-60%.[5-7] In recent years an increasing number of patients are considered eligible for surgical resection of CRLM due to improved treatment strategies, both surgical and non-surgical. These improvements include two-staged liver resections, portal vein embolisation and preoperative systemic therapy downsizing initially unresectable CRLM.[8-10]

In order to predict prognosis of patients with CRLM considered for surgery, various groups have assessed risk factors and multiple prognostic scoring systems have been developed.[11-17] The clinical risk score (CRS) by Fong et al. is the most used scoring system, and its prognostic value has been validated by several independent investigators.[18-21] According to this CRS the following items are assigned one point: positive nodal status of the primary tumour, tumour size >50mm, >1 metastases, CEA-level >200ng/ml and an interval between primary tumour and development of liver metastases <12 months. Patients with extrahepatic disease are excluded. The total sum of the CRS divides patients into 'low risk' (0-2 points), and 'high risk' (3-5 points) of disease recurrence and overall survival after surgery.[18]

Due to extra-hepatic disease and location, number or size of the liver metastases, only a minority of patients is, or will become, eligible for liver resection.[13, 22] There are two issues that play an important role in the treatment of patients with CRLM. First, there is no consensus on the criteria for resectability. Blinded retrospective reviews on this topic illustrated great variability in the assessment of resectability, even between dedicated liver surgeons.[10, 23] Second, chemotherapy regimens combining multiple drugs enriched with targeted agents, resulted in median OS of >30 months in patients with initially unresectable CRLM.[24, 25] Despite these survival rates in patients treated with systemic therapy, there is little doubt that surgical resection of CRLM offers the best chance for long-term survival.[26] [27] A randomised clinical trial on this topic is not considered to be ethical.
So, the challenge remains to identify all patients who may be candidates for radical surgery of CRLM. Although the majority of cancer patients are currently being assessed in

multidisciplinary teams (MDT), specific expertise in liver surgery is often lacking in these teams.
Therefore, we investigated the baseline resectability status in the subgroup of patients with CRLM in two well-defined and prospectively established patient cohorts, who were considered to have unresectable CRLM and received systemic therapy within a clinical trial. The survival of patients who were considered resectable at baseline was compared to a matched control group of patients who underwent surgical resection of CRLM.

Methods

Patient population and data-collection

Patients treated with systemic therapy

We analysed patients with presumed unresectable CRLM at baseline who were included in two phase III randomised clinical trials from the Dutch Colorectal Cancer Group (DCCG). Starting in 2003, the CAIRO study randomised 820 metastatic CRC patients between first-line sequential and a combination treatment with capecitabine, irinotecan and oxaliplatin.[28] The CAIRO2 study included 755 metastatic CRC patients, who were randomly assigned to receive first-line treatment with capecitabine, oxaliplatin, and bevacizumab, or the same schedule with the addition of weekly cetuximab.[29] One of the inclusion criteria in both studies was that the metastases were unresectable. However a discussion of the individual patient in a multidisciplinary liver team was not mandatory for inclusion in both studies. Patients in the CAIRO study were required to have a World Health Organisation (WHO) performance status of 0-2, and in the CAIRO2 study of 0-1. The details of both studies have been presented previously.[28, 29]
Since patients with more than 10 CRLM are rarely candidates for curative surgery, CAIRO and CAIRO2 patients with less than 10 CRLM and without extra-hepatic disease were selected. Patients in both trials who underwent liver resection after initial systemic therapy were excluded, as well as patients with the primary colorectal tumour still in situ. Another criterion for exclusion was incomplete data on the items of the CRS.[18] These criteria were pre-treatment CEA level, number of CRLM, size of the CRLM, lymph node status of the primary tumour, and the time between surgery of the primary tumour and treatment (systemic therapy) of the liver metastases. These data were not necessary to be known for inclusion in the CAIRO and CAIRO2 studies, and therefore were not available in the majority of patients.

Patients treated with liver resection

Radboud University Medical Center Nijmegen and Erasmus Medical Center Cancer Institute Rotterdam are tertiary referral hospitals for CRLM surgery. Post-operative follow-up consisted of clinical examination, measurement of CEA levels, and imaging using computed tomography (CT). In order to compare patients from similar time periods, all patients who underwent primary liver resection for CRLM between January 2003 (start of the CAIRO study) and September 2011 were analysed in the present study. Patients who received induction, neo-adjuvant systemic therapy were excluded from the present analyses. Patients who underwent liver resection together with radio frequent ablation (RFA) of other lesions during the same operation were also excluded. Liver resection was considered to be complete (R0) when the pathologist assessed free resection margins.

Data-collection and matching

Demographics and clinical-pathological factors of the primary tumour and the liver metastases were collected. Fong's CRS was used for matching patients' oncological risk profiles.[18] Therefore, all five variables included in this CRS were collected: CEA level, tumour size and number of metastases recorded at baseline, the disease-free interval between resection of the primary tumour and treatment of liver metastases (either surgery or randomisation for systemic therapy) and nodal status of the primary tumour. Systemically treated patients were selected and case-matched to patients who underwent liver resection only, in terms of gender, age, CRS and the absence of extra-hepatic metastases.

Review of resectability

In order to assess the potential surgical options and agreement on proposed treatment for CRLM, all baseline CT-scans of patients treated with systemic therapy were requested. Review of resectability, based on radiological images only, was performed by 3 dedicated liver surgeons. After reviewing the images of the CT-scans, liver lesions were classified:

- resectable
- complex resectable (e.g. two-staged procedures, including portal vein embolisation, resection in combination with RFA, or the need for induction chemotherapy)
- unresectable
- CT-images were of insufficient quality for the assessment of resectability. Quality of images was based on the system used by Jones et al.[23]

Outcome variables

The primary end-point of the current analysis was OS. This was defined as the time from liver resection or from randomisation to systemic therapy, until date of last follow-up or death. As described in the protocols of CAIRO and CAIRO II, the maximum time to start systemic treatment had to be within 7 days from randomisation.[28, 29]

Statistical analyses

The comparison between categorical variables was performed using the chi-square tests. Means and medians of the items from the CRS were compared using the Mann-Whitney-U test. Survival analyses were performed by using the Kaplan Meier survival analysis, and compared by using log-rank tests. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 18.0 (SPSS, Inc., Chicago, Illinois, USA).

Results

Patients and treatment characteristics

Systemic therapy

A total of 480 patients with CRLM, without extra-hepatic metastases, were treated with systemic therapy between January 2003-December 2004 (CAIRO, *n*=256) and between June 2005-December 2006 (CAIRO2, *n*=224). The majority of patients (*n*=259; 54%) could not be included in the present study due to missing or incomplete data with respect to the clinical risk score items. The CEA-level before starting systemic treatment was most frequently absent. Other reasons for exclusion are listed in Figure 1a. Eventually 36 patients were eligible for inclusion from either the CAIRO (*n*=14), or CAIRO2 (*n*=22). Of these 36 patients, six patients were treated with first-line sequential chemotherapy, eight patients received first-line combination therapy, 16 patients were treated with first-line chemotherapy with bevacizumab, and six patients received first-line chemotherapy in combination with bevacizumab and cetuximab.

Retrospective review of resectability

Baseline CT images of 57 patients (out of 96 patients selected from the CAIRO studies) could be retrieved from the different hospitals. These images were not available in 39 patients, because they were stored on microfilm only, or not stored digitally. In one patient, all three surgeons considered the CT images of "insufficient quality for review", which left 56 patients (58.3%) eligible for analyses. In five patients one or more surgeons were unable to make a decision on resectability as a result of insufficient quality of the CT images. The majority of patients were considered (complex) resectable (*n*=36; 64.2%), while only two patients were considered unresectable by all three reviewers (Figure 2).

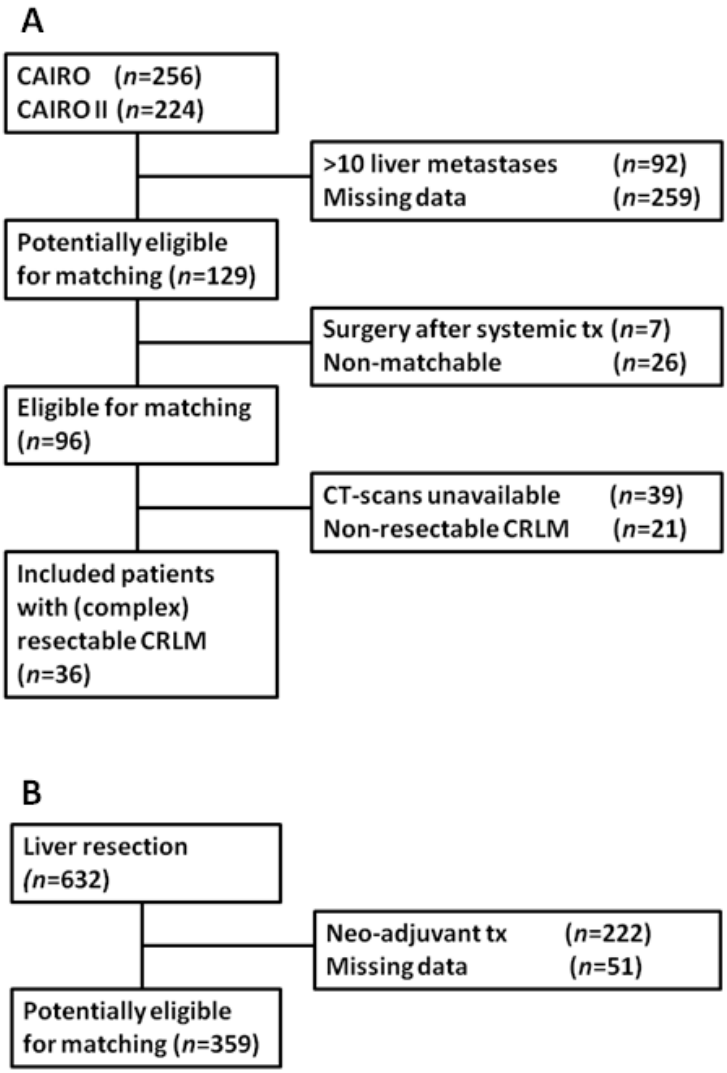

Figure 1A. Selection process of patients with colorectal liver metastases treated with systemic therapy. Tx: treatment. CRLM: colorectal liver metastases. **Figure 1B.** Selection process of patients with colorectal liver metastases treated with liver resection. Tx: treatment; CRS: clinical risk score.

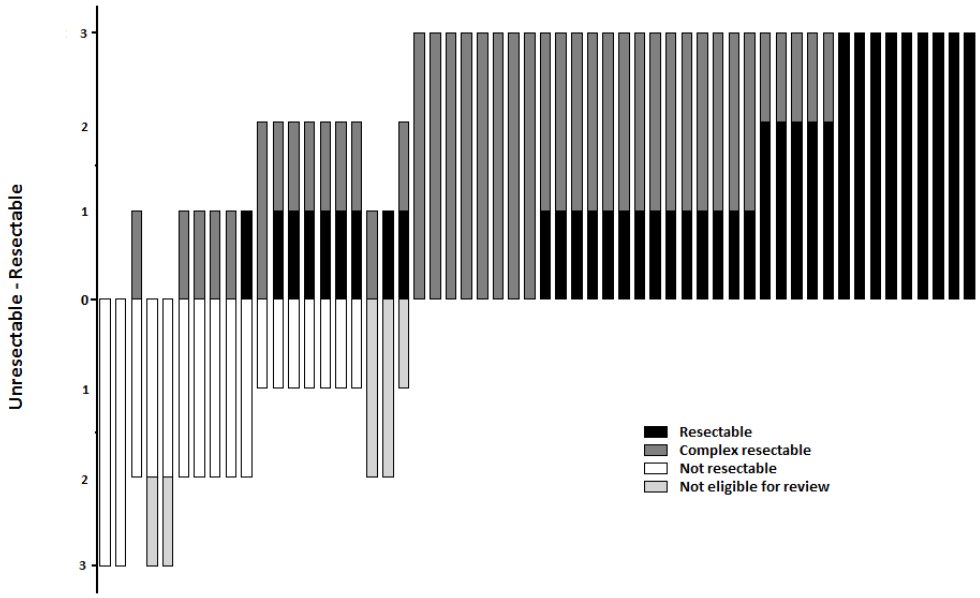

Figure 2. Plot showing decisions of three surgeons on resectability of colorectal liver metastases in 56 patients who were treated with systemic therapy, based on computer tomography images. The number of reviewers who made a decision is shown on the Y-axis and each bar on the X-axis represents one patient.
Complex resectability was defined as the need for neo-adjuvant treatment or complex surgery (two-staged procedures including portal vein embolisation or resection in combination with radiofrequent ablation).

Liver resection

A total of 632 patients underwent liver resection between January 2003 until September 2011. After excluding patients treated with neo-adjuvant systemic treatment (*n*=222), patients of whom data were missing on one of the items of the CRS (*n*=25), or patients with extra-hepatic disease (*n*=26), 359 patients were eligible and could be included in the current study.

Case-matching

A total of 36 patients who were considered (complex) resectable by the liver surgeons were matched with patients who underwent liver surgery. The clinical-pathological characteristics used to case-match both treatment groups are summarised in Table 1. The types of performed liver resection were: wedge resection (*n*=15); segmental resection (*n*=11); hemihepatectomy (*n*=10). A microscopic incomplete resection (R1) seemed to be present in 6 patients (16.7%). After resection, seven patients (19.4%) were treated with adjuvant systemic therapy (fluoropyrimidine only (*n*=1) and fluoropyrimidine plus oxaliplatin (*n*=6)), of which, 1 patient was also treated with bevacizumab as part of a multicentre randomized clinical trial.[30]

Table 1. Demographic, tumour and clinical-pathological factors of case-matched patients treated with systemic therapy or liver resection. CEA: carcinoembryonic antigen

		Systemic therapy *n*=36	Surgery *n*=36	*p*-value
Gender				
Male		20 (55.6%)	20 (55.6%)	
Female		16 (44.4%)	16 (44.4%)	
Median age in years (range)		66.5 (36-79)	66 (32-79)	0.813
Primary tumour				
Colon		29 (80.6%)	22 (61.1%)	**0.023****
Rectum		5 (13.9%)	14 (38.9%)	
Unknown		2 (5.5%)	0	
T-stage primary tumour				
T1-3		26 (72.2%)	30 (83.3%)	0.257
T4		10 (27.8%)	6 (16.7%)	
Lymph node				
Negative		16 (44.4%)	11 (30.6%)	0.224
Positive		20 (55.6%)	25 (69.4%)	
Liver metastases				
Median CEA level (range)		18.5 (1-635)	26.6 (1-910)	0.907
Median interval (range)*		4 (1-109)	3 (0-91)	0.907
Median number metastases (range)		4 (1-7)	3 (1-10)	**0.009****
Median size largest metastasis in mm (range)		30 (12-160)	39 (12-120)	**0.044****
Fong-score[18]	1	5 (13.9%)	4 (11.1%)	0.907
	2	10 (27.8%)	12 (33.3%)	
	3	18 (50.0%)	16 (44.5%)	
	4	3 (8.3%)	4 (11.1%)	

* Interval between treatment of the primary tumour and the liver metastases (either systemic therapy or liver resection)
** and in bold: significant with $p<0.05$

Survival

Median follow-up of all patients treated with systemic therapy was 43 months (range: 0-81 months) and 31 months (range: 0-101 months) for patients who were surgically treated.

Median OS in the total group of patients treated with systemic therapy (*n*=480) was 21 months (range: 0-84 months), and 52 months (range: 0-101 months) in the total group of patients who underwent liver resection (*n*=632). The 5-year OS was 11.9% in patients treated with systemic therapy only versus 45.6% in surgically treated patients.

In the matched cohort of patients treated with systemic therapy (*n*=36) median OS was 27 months (range: 0-81 months), which was significantly higher (*p*=0.002) than in the total group of patients treated with systemic therapy (*n*=480). However, the OS in the matched cohort of patients treated with systemic therapy was significantly lower (*p*=0.027) compared

to the median OS of 56 months (range: 1-116 months) in case-matched patients treated with liver resection (*n*=36) (Figure 3).

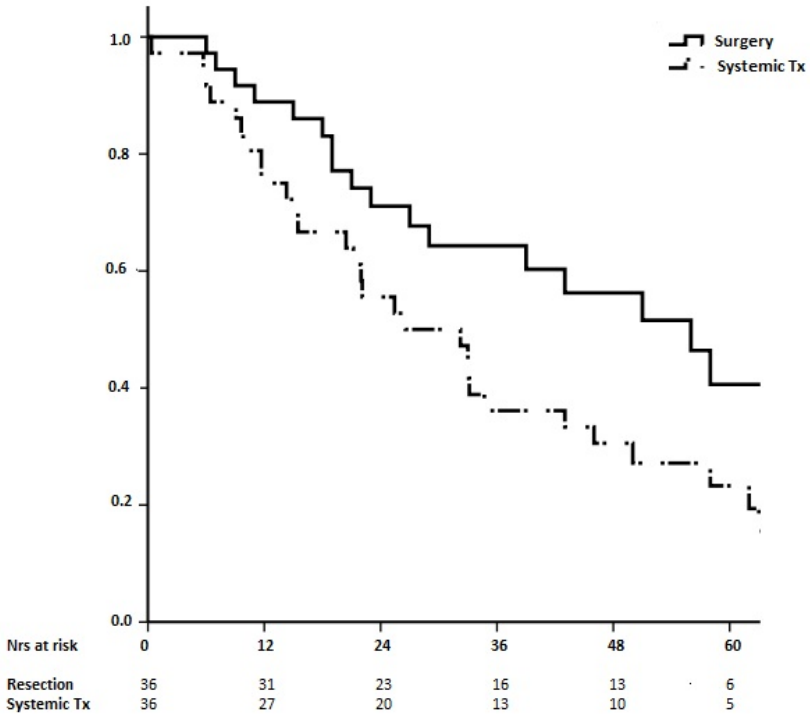

Figure 3. Overall survival in case-matched patients with colorectal liver metastases (considered resectable based on reviewing the computed tomography images) treated with either systemic therapy or liver resection (*p*=0.027). On the Y-axis the proportion of patients, on the X-axis survival in months. Tx: treatment. Nrs: numbers

Discussion

This study showed that patients with CRLM are not always identified and offered surgery with curative intent. In the retrospective evaluation of CT images performed by dedicated liver surgeons in a patient group treated with systemic, palliative regimens for CRLM, a significant number appeared to be resectable. The case-matched patient groups with resectable liver only disease showed significant differences in OS after surgical or systemic treatment strategies. Patients undergoing surgery for CRLM had superior OS rates, as compared to patients in whom systemic therapies were administered. The current study suggests that surgery is the preferred treatment strategy in patients with CRLM. These findings emphasise the importance of adequate patient selection for surgery.

In the current study, patients were selected from two completed multicentre randomised clinical trials focusing on systemic therapy for CRLM, and from two large liver surgery databases. On ethical grounds, a true randomised clinical trial comparing both treatment strategies in patients with resectable CRLM has not been, and will not be performed. By case-matching the patients for known prognostic factors, this study is the second best alternative to compare both treatment strategies in patients with resectable CRLM.

After liver surgery a significantly longer OS (median 56 months) was demonstrated compared to treatment with systemic therapy for (retrospectively) resectable liver metastases (median 27 months).

Kopetz et al. (2009) previously reported a survival benefit in patients with CRLM who underwent liver resection compared to patients treated with systemic therapy.[26] Patients undergoing liver surgery in that study received pre-operative systemic therapy, which we excluded in the present study. Also, data were derived from unmatched patient cohorts, which could make the results susceptible for additional bias and should be interpreted cautiously. Brouquet et al. (2011) performed an intention-to-treat analysis to evaluate OS of 'high risk patients' with CRLM (patients undergoing at least the first stage of a two-staged surgical approach) after treatment with systemic agents versus patients treated with systemic therapy only.[27] In the surgery group, only non-progressors on systemic therapy were selected for comparison. In the group of patients treated with systemic therapy only, responders were selected, suggesting that only patients with favourable tumour biology were used for comparison. This could induce a potential bias for the survival rates demonstrated in the group of patients receiving systemic therapy only (favourable tumour biology). However, even though patients with excellent response to systemic therapy were selected for comparison, surgery proved to yield superior OS.

In the present study patients who underwent neo-adjuvant systemic therapy were excluded to prevent a potential bias selecting only these patients who did not progress on systemic therapy. On the other hand, a recent study by Ayez et al. describing 363 patients who underwent liver surgery showed no significant difference in median OS between patients who did or did not receive neo-adjuvant systemic therapy in low risk patients (CRS ≤2 points).[31] Patients with a high risk profile (CRS >2) had a significant survival benefit after neo-adjuvant systemic therapy (46 months versus 33 months).[31] By including and matching patients who underwent systemic therapy followed by surgery, survival will probably only be slightly different (perhaps higher) in the surgery group. Despite this, the effect of neo-adjuvant or adjuvant systemic therapy remains subject of many debates, since data from the EPOC study did not show an OS difference[32], while Rahbari et al. and Ayez et al. demonstrated only a potential effect of (neo-) adjuvant therapy in high risk CRC patients.[31, 33]

For this reason a randomised clinical trial was recently started in the Netherlands comparing neo-adjuvant systemic therapy, followed by surgery versus surgery alone in high risk CRC patients.[34]

In the group of patients treated with systemic therapy only, patients with favourable characteristics (< 10 liver only metastases) were selected from the CAIRO studies. This was demonstrated by a median OS of 27 months, which was significantly higher compared to the complete group of patients with treated with systemic therapy in both CAIRO studies (21 months; p=0.002).[28, 29] Moreover, it has been previously demonstrated that patients treated in the CAIRO studies or outside the study but with similar therapeutic drugs have a better survival than patients not treated with these medications.[35] Matching of the surgical and systemic patient groups was performed using the CRS, age and gender. After case-matching, the OS of systemically treated patients with resectable CRLM (based on reviewing the CT images, n=36), was compared to the OS of patients who underwent liver resection. Median OS was 56 months (range: 1-101 months) in patients who were treated with liver resection, which was superior compared to systemically treated patients (median OS 27 months; range: 0-81) (p=0.027). Moreover, 5-year survival in the surgically treated group was 46.4% which is comparable to survival rates in the literature after liver resection with a median OS of 43-64 months and 5-year OS rates of 51%-58%.[7, 36] The results of this study support the concept of a surgical treatment strategy as the gold standard for CRLM, although this has never been validated in a prospective randomised clinical trial.

Unfortunately, there was no information available whether patients treated with systemic therapy only were discussed in multi-disciplinary teams (MDT), and evaluated for potential resectability. Jones et al. reported the importance of MDTs, and especially the involvement of specialist liver surgeons in those teams.[23] In their study, 63% of the patients with liver only CRLM, who were treated with palliative systemic treatment, were retrospectively considered to have potentially resectable CRLM by a majority of the reviewing liver surgeons. In the present study the CT images of the systemically treated patients were reviewed and at least two out of three liver surgeons agreed on CRLM being resectable in 79% of cases. On the other hand, this analysis was retrospectively performed and a more aggressive treatment strategy by surgeons over time could also be an important factor for this difference. This has been demonstrated by a recent study from the Netherlands showing a significant increase in the number of patients undergoing liver surgery for metastatic disease in the last decade.[37]

In the CAIRO studies only 4.8% (n=23) of all systemically treated patients with liver only metastases underwent subsequent liver resection after a good response. For the comparison of survival in the present study, patients were only included if they continued systemic treatment and if they did not undergo liver surgery or other local therapies. Data from the CLOCC trial demonstrated that patients treated with RFA as local ablative therapy showed an improved disease-free survival and a trend towards improved OS.[38] Importantly, the decision on whether to perform a liver resection for CRLM is subject to bias as

demonstrated by 13 of 56 patients (23.2%) in which at least one of the liver surgeons (being the expert panel of this study) considered liver lesions unresectable, while one of the other surgeons considered the same lesions (potentially) resectable. Folprecht et al. (2010) previously demonstrated critical disagreement between experienced liver surgeons in 7% of assessed patients, when they evaluated resectability on CT images of patients and decided whether surgery or (induction) chemotherapy was the preferred treatment strategy.[10]

These results of the present study emphasise the importance of assessing each patient with CRLM by a dedicated MDT, including specialised liver surgeons. Structural assessment of all patients with CRLM by specialist teams, might ensure that potentially all that qualify for surgery are identified as such, offering those patients the best prospects in terms of survival. A useful tool to assess resectability might be the Met-Assist program, which was developed to indicate the likelihood that experts in the field would judge surgery as feasible under given circumstances.[39, 40] Currently, the CAIRO5 trial is performed in which patients with potentially resectable CRLM are selected for different induction chemotherapy regimens.[39] This prospective trial uses a central panel consisting of one radiologist and three liver surgeons. Possibly, this trial will add to the definition of resectability of CRLM in the future.
Apart from the (retrospective) observation that resection for CRLM yields superior survival rates as compared to systemic therapy; another point of interest is the cost effectiveness of treatment strategies. Recently, Roberts et al. performed a cost-utility analysis of operative versus non-operative treatment for CRLM.[41] The results of their study show surgery is more effective and less costly than non-operative treatment for CRLM. Again, this emphasises the importance of patient selection for resection.
A limitation of the present study may be that patients who underwent systemic therapy in the CAIRO and CAIRO2 trial underwent CT imaging demonstrating liver only disease, but did not all receive additional diagnostics for extra-hepatic metastases (e.g. fluoro-deoxyglucose (FDG) positron emission tomography (PET)-scan). A recent randomised clinical trial evaluating the treatment changes in patients with CRLM scheduled for surgery after FDG-PET CT-scan, reported cancellation of the suggested surgical procedure in only 2.7% of the patients.[42] Additionally, survival in patients who underwent liver surgery did not differ between patients who were selected with or without FDG-PET.[43] Because of the retrospective character of the current study and despite the thorough case-matching, the performance status and co-morbidity may differ between surgery and systemically treated patients. However, the systemically treated patients all had a WHO performance status of 0-2 in the CAIRO study and WHO status of 0-1 in the CAIRO2 study, which is probably not inferior to the surgically treated patients.
Despite the case-matching based on gender, age and the CRS by Fong et al.[18], there is still an imbalance between the two patient cohorts. Patients who were treated with systemic

therapy were considered 'complex resectable' in most of the patients (*n*=25; 69%), while most of the patients in the surgical cohort were treated with a segmentectomy or wedge resection (*n*=26; 72%). Also, in patients who were treated with systemic therapy were considered 'resectable' on the basis of reviewing the CT-scan, and especially in complex resectable patients there is always a risk that the liver resection is not possible, e.g. due to small liver metastases that were not detected by CT-scan, or no liver hypertrophy after portal vein embolisation.

Another limitation is that patients were included in the CAIRO studies from 2003-2006, whereas patients who underwent liver surgery were selected from a liver database from 2003-2011. Although some patients in this study have been operated on more recently, it is unlikely that this explains the differences in OS demonstrated in the present study.

In conclusion, this case-matched controlled comparison of patients undergoing either systemic therapy or surgery for resectable CRLM demonstrates a significant survival benefit in patients treated with liver resection. Surgery should remain the gold standard treatment for patients with CRLM. This finding emphasises the importance of adequate patient selection for surgery. Consensus on resectability and standardised assessment of all patients presenting with CRLM by dedicated liver surgeons in specialised MDTs optimises patient selection for surgery.

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CHAPTER 7

Preoperative FDG-PET-scan in patients with resectable colorectal liver metastases does not improve overall survival: a retrospective analysis stratified by clinical risk score

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Abstract

Background: The aim of this study was to determin whether the selection with fluorine-18-deoxyglucose positron emission tomography (FDG-PET) imaging would result in an improved outcome in surgically treated patients with curative resection of colorectal liver metastases (CRLM), stratified by the clinical risk score (CRS) of Fong et al. (Ann Surg 1999; 230:309-318).

Patients and methods: Between January 2000 and December 2009, all patients who underwent resection for CRLM from two different university teaching hospitals in the Netherlands were analysed. Patients were stratified by the clinical risk score (CRS).

Results: In total 613 patients were eligible for analyses. There was no statistical difference in median disease-free survival (DFS) between patients with and without an FDG-PET-scan in both low CRS [17 months (95%CI: 12-22) versus 14 months (95% CI: 11-17), p=0.332] and high CRS [14 months (95% CI: 7-21) versus 9 months (95% CI: 8-10), p=0.073]. There was no statistical difference in median overall survival (OS) between patients with and without a FDG-PET-scan in both low CRS [64 months (95% CI 54-74) versus 54 months (95% CI 42-66), p=0.663] and high CRS [39 months (95% CI 23-55) versus 41 months (95% CI 34-48), p=0.903].

Conclusion: The present study could not demonstrate that patients selected by an FDG-PET-scan before liver resection, and stratified by the CRS have an improvement in DFS or OS.

Introduction

Colorectal cancer is one of the leading causes of cancer death worldwide.[1] Approximately half of the patients with colorectal cancer will develop metastatic disease at some point during the course of the disease. If metastases are confined to the liver, resection of these metastases is at present the standard of care and it has a positive impact on survival.[2,3] After a curative resection of colorectal liver metastases (CRLM), cancer relapse is a common phenomenon, with approximately 50% of recurrences occurring in the first 2 years.[4] In general, 5-year overall survival ranges between 20-60%, depending on tumour and patient characteristics. In an attempt to identify subgroups with a variable risk for relapse and survival, several clinical risk scores (CRS) have been introduced.[5-9] The most widely used CRS was described by Fong et al.[10] and the prognostic value of this scoring system has been verified by independent investigators.[11-13]

Preoperative staging is important for the selection of patients who can potentially undergo resection of CRLM. To identify the number and location of colorectal metastases, contrast-enhanced CT or MRI of the liver is generally used. In addition, an abdominal and chest CT is usually performed to exclude extrahepatic disease. To further improve the selection of patients for surgery, fluorine-18-deoxyglucose positron emission tomography (FDG-PET) has been assessed in patients with CRLM.[14] Some studies suggest that a change in clinical management could be expected after FDG-PET, whereas other authors claim that the addition of staging with an FDG-PET/CT prior to planned liver resection has substantially less impact on surgical management than expected.[14-16] If FDG-PET is able to identify the patients with extrahepatic disease who are unlikely to benefit from liver resection, patients with a negative extrahepatic FDG-PET should represent a selected subgroup that is more likely to benefit from surgery. This might be reflected in an improved disease- free survival (DFS) and possibly overall survival compared to patients who have not undergone preoperative staging with FDG-PET. In the present study we analysed whether this selection with FDG-PET would result in an improved outcome in surgically treated patients with CRLM, stratified by the CRS of Fong et al.[10]

Patients and methods

Between January 2000 and December 2009, all patients who underwent liver resection for CRLM from two different university teaching hospitals in the Netherlands were analysed retrospectively. In these two hospitals more than a quarter of all colorectal liver metastases undergo surgery. Patients were assessed with the CRS according to Fong et al.[10] and excluded from the analyses if they had missing data required to calculate the CRS. The criteria that

are incorporated in this CRS system are: (1) nodal status of primary, (2) disease-free interval from the primary to discovery of the liver metastases <12 months, (3) number of tumours >1, (4) size of the largest tumour >5 cm, and (5) preoperative carcinoembryonic antigen (CEA) level >200 ng/ml.[10] Each criterion is assigned 1 point in this CRS and we defined two risk groups: low CRS (0-2 risk factors) and high CRS (3-5 risk factors).

Treatment protocol

The Erasmus MC University Medical Center Rotterdam and Radboud University Nijmegen Medical Center are tertiary referral hospitals for CRLM. All patients were discussed in multidisciplinary tumour boards. In their protocols, perioperative chemotherapy is not considered standard of care in all patients with primarily resectable CRLM (i.e. the possibility of an R0 resection, the vascular inflow and outflow must be secured, as well as biliary drainage to the remaining segments, and a future liver remnant of at least 20-30%).

Patients receive neo-adjuvant chemotherapy in case liver metastases are initially unresectable or difficult to resect (due to adverse location or being close to vascular or biliary structures) or when multiple (≥4) synchronous metastases are present.

A large proportion of patients in this study already had already received neo-adjuvant chemotherapy in the referring hospitals, according to local treatment protocols. Patients treated with neo-adjuvant chemotherapy received a combination of 5-fluorouracil/capecitabine and oxaliplatin or irinotecan, with or without bevacizumab. The response to neo-adjuvant chemotherapy was assessed after 2 or 3 cycles by CT scan and CEA levels. Further treatment was considered depending on tumour response and extent of the disease. If liver metastases were considered resectable, a laparotomy was planned at least 3 weeks after the last course of systemic neo-adjuvant chemotherapy. Bevacizumab had to be excluded from the last course of chemotherapy to ensure an interval of at least 6 weeks.

FDG-PET was performed within 5 weeks before surgery in a selection of patients, based on a multicentre study or by physician's choice. The abdomen was examined at laparatomy for extrahepatic disease. In case of extrahepatic disease (confirmed by frozen sections) any further surgical treatment was only carried out if all tumour deposits could be resected. A minority of patients received adjuvant chemotherapy as part of a trial in the Netherlands (HEPATICA) irrespective whether or not preoperative FDG-PET was performed.[17] Post-operative follow-up consisted of a clinical examination and measurement of CEA every 3 months. In the Erasmus MC University Medical Center Rotterdam, abdominal imaging (ultrasound, CT of the chest and abdomen) was usually performed every 3 months in the first year and every 6 months the second year and once per year thereafter. In the Radboud University Nijmegen Medical Center this was every 3 months in the first 3 years and every 6 months in the 4th and 5th year. If recurrent disease occurred, a decision on further treatment, surgical or systemic, was made by the multidisciplinary tumour board.

FDG-PET Imaging

Patients fasted for at least 6 hours and were hydrated with sugar-free liquids. Patients received a dose of approximately 4 MBq of 18-F-FDG per kilogram of body weight. Scans were acquired 60–90 min after 18-F-FDG injection and processed according to the protocols of the respective center. All scans were visually analysed by experienced nuclear medicine physicians. Standardised uptake values were not calculated. At the time when the data were collected, integrated PET/CT scanners were not available in the participating centers.

Outcome

Overall survival (OS) was defined as the interval in months between resection of CRLM and death, or the date of last follow-up. Disease-free survival (DFS) was defined as the interval in months between resection of CRLM and recurrence, death without recurrence, or date of last follow-up without recurrence.

Statistics

Descriptive values are expressed as median with the interquartile range (IQR). Comparison between categorical variables was determined by the chi-square test. Survival analysis was performed by the Kaplan-Meier method. Comparison between survival curves was made by log-rank tests. Univariate analysis was performed with Cox regression analysis. For the multivariate analysis only parameters with a p value <0.10 in the univariate model were entered into the Cox regression model. Backward elimination was applied. Variables were included if p-values were ≤0.05 and were removed if p-values were >0.10. The SPSS statistical package version 17.0 (SPSS, Inc., Chicago, Illinois, USA) was used for statistical analysis, where a p-value of <0.05 was considered statistically significant.

Results

Between January 2000 and December 2009, 665 patients underwent liver resection for CRLM. Of these, 52 patients (8%) were excluded due to missing data for calculation of the CRS, leaving 613 patients eligible for analyses.

Neo-adjuvant chemotherapy was given in 196 (32%) patients. The median number of chemotherapy cycles was 6 (IQR 4-7). Adjuvant chemotherapy was administered in 41 patients (7%). Patient and tumour characteristics were statistically comparable between both groups. PET scans were significantly more often performed in patients with a longer interval between primary tumour and liver resection, and in patients with a low CRS. Patients in the non-PET group received significantly more often chemotherapy. The patient characteristics are displayed in Table 1.

Table 1: Characteristics of patients with and without FDG-PET scan.

	With FDG-PET scan (*n*=206)	**Without FDG-PET scan (*n*=407)**	***p*-value**	**All participants (*n*=613)**
Male	119 (58)	262 (64)	0.111	381 (62)
Median age, years	62 (57-70)	64 (57-70)	0.236	63 (57-70)
Rectal cancer	79 (38)	173 (43)	0.323	252 (41)
Primary tumour characteristics				
T stage			0.624	
T3	149 (72)	293 (72		442 (72)
T4	18 (9)	41 (10)		59 (10)
Positive lymph node	126 (61)	223 (55)	0.132	349 (57)
CEA, ug/L			0.181	
Median	10.6 (3.3-28.6)	71.0 (5.6-61.3)		15.0 (4.7-50.5)
Mean	60.8	99.9		86.7
Liver metastases				
Interval>12 months	116 (56)	266 (65)	**0.029****	382 (62)
Diameter, cm			0.141	
Median	3.5 (2.0-4.6)	3.4 (2.2-5.0)		3.4 (2.2-5.0)
Metastases, *n*			0.061	
Median	1 (1-3)	2 (1-3)		2 (1-3)
Bilobar	71 (34)	148 (36)	0.628	219 (36)
R1 resection	39 (19)	75 (18)	0.680	114 (19)
Extrahepatic disease	9 (5)	35 (8)	0.055	44 (7)
Chemotherapy	54 (26)	179 (44)	**<0.001****	233 (38)
CRS			**0.033****	
Low	146 (71)	253 (62)		399 (65)
High	60 (29)	154 (38)		214 (35)

CEA: carcinembryonic antigen; CRS: clinical risk score. Values in parentheses are either percentage or IQR; ** Bold indicates $p<0.05$

DFS and recurrence

The median follow-up was 36 months (IQR 22-59). During follow up, 414 patients (68%) developed a recurrence. For patients with a low CRS the median DFS was 15 months (95% CI: 12-18) and for patient with a high CRS it was 9 months (95% CI: 7-11), $p<0.001$. DFS was influenced by tumour distribution in low CRS patients and by the number of metastases in high risk patients after multivariate analysis. Chemotherapy did not influence DFS in this study. There was no statistical difference in median DFS between patients with and without an FDG-PET-scan in both low CRS [17 months (95% CI: 12-22) versus 14 months (95% CI: 11-17), $p=0.332$] and high CRS [14 months (95% CI: 7-21) versus 9 months (95% CI: 8-10), $p=0.073$] (Figure 1).

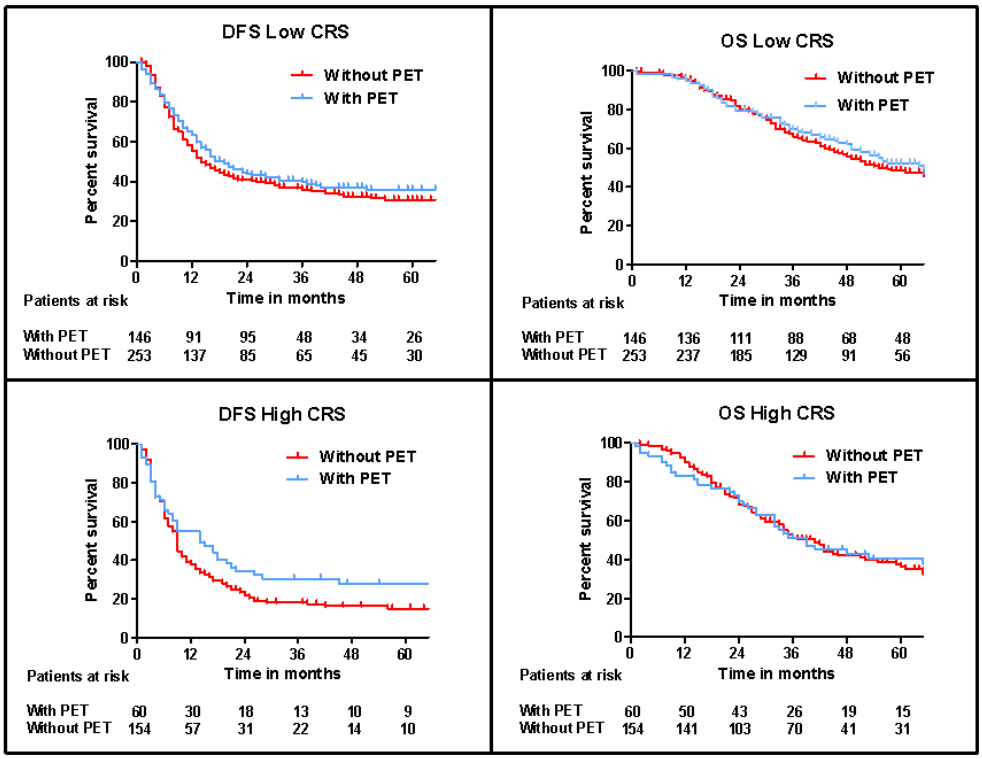

Figure 1. Disease-free survival (DFS) and overall survival (OS) in patients after liver resection with a low and high clinical risk score (CRS) with or without pre-operative FGD-PET scan.

Overall Survival

For patient with a low CRS the median OS was 57 months (95% CI: 49-65) and for patients with a high CRS it was 39 months (95% CI: 34-44), p=0.004. OS was influenced by the tumour stage of the primary tumour in low-CRS patients and by age, tumour distribution and chemotherapy in high-CRS patients after multivariate analysis. There was no statistical difference in median OS between patients with and without a FDG-PET-scan in both low CRS [64 months (95% CI 54-74) versus 54 months (95% CI 42-66), p=0.663] and high CRS [39 months (95% CI 23-55) versus 41 months (95% CI 34-48), p=0.903] (Figure 1). The univariate and multivariate analyses for DFS and OS are depicted in Tables 2 and 3.

Table 2. Univariate and multivariate analyses: disease-free survival.

Variable	Low CRS					High CRS				
	Median Survival	Univariate HR	*p*-value	Multivariate HR	*p*-value	Median survival	Univariate HR	*p*-value	Multivariate HR	*p*-value
Gender		0.83 (0.64-1.07)	0.146	NS			1.01 (0.74-1.37)	0.969	NS	
Female	14 (11-17)					8 (6-10)				
Male	16 (12-20)					9 (7-11)				
Age		0.85 (0.65-1.10)	0.207	NS			1.20 (0.88-1.64)	0.248	NS	
< 60	13 (10-16)					9 (7-11)				
≥ 60	17 (13-21)					9 (7-11)				
Primary tumour		0.86 (0.67-1.09)	0.212	NS			0.94 (0.69-1.28)	0.707	NS	
Colon	17 (12-22)					9 (7-11)				
Rectum	13 (10-16)					9 (7-11)				
T stage tumour		1.47 (0.99-2.17)	0.057	NS			1.44 (0.91-2.29)	0.117	NS	
T1-3	16 (13-19)					9 (7-11)				
T4	13 (8-18)					9 (5-13)				
Lymph node		1.12 (0.87-1.43)	0.377	NS			1.10 (0.71-1.69)	0.670	NS	
Negative	16 (12-20)					11 (6-16)				
Positive	15 (11-19)					9 (8-10)				
Liver metastases										
Time diagnosis (months)		1.12 (0.88-1.44)	0.336	NS			0.97 (0.57-1.65)	0.907	NS	
> 12	16 (11-21)					8 (4-12)				
≤ 12	14 (12-16)					9 (7-11)				
Metastases (*n*)		1.54 (1.11-2.13)	**0.010**	NS			1.51 (1.11-2.05)	**0.009**	1.51 (1.07-2.05)	**0.009**
< 4	17 (13-21)					10 (7-13)				
≥ 4	11 (8-14)					8 (6-10)				

Largest metastasis	size	1.32 (0.70-2.45)	0.393	NS			1.03 (0.81-1.29)	0.835	NS
< 5 cm	16 (13-19)					9 (8-10)			
≥ 5 cm	14 (10-18)					9 (5-13)			
Tumour distribution		1.74 (1.33-2.27)	**<0.001**	1.71 (1.29-2.27)	**<0.001**		1.24 (0.91-1.69)	0.172	NS
Unilobar	19 (13-25)					9 (6-12)			
Bilobar	10 (7-13)					9 (7-11)			
CEA level (ug/L)		1.62 (0.86-3.04)	0.137	NS			1.12 (0.77-1.64)	0.551	NS
< 200	15 (12-18)					9 (8-10)			
≥ 200	12 (4-20)					7 (4-10)			
Resection margin		1.35 (0.96-1.91)	0.088	NS			1.27 (0.90-1.80)	0.178	NS
R0	16 (12-20)					10 (8-12)			
R1	11 (8-14)					8 (6-10)			
Chemotherapy		1.08 (0.82-1.42)	0.561	NS			1.01 (0.75-1.37)	0.936	NS
No	17 (13-21)					9 (7-11)			
Yes	12 (9-15)					9 (7-11)			
FDG-PET-scan		0.88 (0.68-1.14)	0.341	NS			0.73 (0.51-1.04)	0.084	NS
No	14 (7-11)					9 (8-10)			
Yes	17 (12-22)					14 (7-21)			

CRS: clinical risk score; HR: hazard ratio; NS: not significant; CEA: carcinoembryonic antigen. Values between parentheses are 95% CI. Univariate parameters with a *p*-value <0.10 were included in multivariate analysis. Bold indicates statistical significance with $p<0.05$

Table 3. Univariate and multivariate analyses: overall survival.

Variable	Low CRS					High CRS				
	Median Survival	Univariate HR	*p*-value	Multivariate HR	*p*-value	Median survival	Univariate HR	*p*-value	Multivariate HR	*p*-value
Gender		0.99 (0.74-1.32)	0.933	NS			0.96 (0.68-1.37)	0.832	NS	
Female	56 (45-67)					35 (27-43)				
Male	58 (44-72)					42 (33-51)				
Age		1.07 (0.79-1.43)	0.679	NS			1.52 (1.05-2.19)	**0.026**	1.52 (1.05-2.20)	**0.027**
< 60	64 (55-74)					55 (32-78)				
≥ 60	56 (41-71)					35 (30-40)				
Primary tumour		0.96 (0.73-1.28)	0.787	NS			1.02 (0.71-1.47)	0.903	NS	
Colon	58 (45-71)					39 (28-50)				
Rectum	55 (44-66)					39 (32-46)				
T stage tumour		1.96 (1.31-2.95)	**0.001**	1.99 (1.32-2.99)	**0.001**		1.69 (1.01-2.83)	**0.044**	NS	
T1-3	65 (55-75)					42 (34-50)				
T4	33 (24-42)					27 (19-35)				
Lymph node		1.28 (0.97-1.69)	0.081	NS			1.38 (0.79-2.41)	0.253	NS	
Negative	66 (53-79)					46 (NR)				
Positive	49 (44-54)					39 (33-45)				
Liver metastases										
Time diagnosis (months)		1.06 (0.80-1.40)	0.680	NS			0.84 (0.46-1.52)	0.562	NS	
> 12	64 (50-78)					34 (28-40)				
≤ 12	52 (38-66)					41 (34-48)				
Metastases (*n*)		1.26 (0.87-1.85)	0.226	NS			1.26 (0.88-1.80)	0.208	NS	
< 4	58 (49-67)					43 (31-55)				
≥ 4	45 (28-62)					34 (23-45)				

Largest metastasis size		1.08 (0.75-1.57)	0.679	NS		1.39 (0.98-1.98)	0.064	NS	
< 5 cm	58 (50-66)				43 (32-54)				
≥ 5 cm	49 (32-66)				32 (25-39)				
Tumour distribution		1.16 (0.85-1.59)	0.346	NS		1.36 (0.95-1.95)	0.097	NS	
Unilobar	57 (46-68)				46 (22-70)				
Bilobar	52 (35-69)				35 (29-41)				
CEA level (ug/L)		1.23 (0.58-2.63)	0.588	NS		0.97 (0.63-1.51)	0.896	NS	
< 200	57 (49-65)				39 (33-45)				
≥ 200	36 (23-49)				43 (23-63)				
Resection margin		1.32 (0.89-1.95)	0.165	NS		2.82 (0.35-22.8)	0.325	NS	
R0	65 (54-76)				43 (31-55)				
R1	53 (36-70)				35 (26-44)				
Chemotherapy		1.02 (0.74-1.40)	0.903	NS		0.65 (0.46-0.96)	**0.016**	0.63 (0.44-0.89)	0.010
No	61 (52-70)				34 (28-40)				
Yes	47 (65)				65 (33-97)				
FDG-PET-scan		0.94 (0.71-1.25)	0.665	NS		1.02 (0.70-1.50)	0.904	NS	
No	54 (42-66)				41 (34-48)				
Yes	64 (54-74)				39 (23-55)				

CRS: clinical risk score; HR: hazard ratio; NS: not significant; NR: not reached; CEA: carcinoembryonic antigen. Values between parentheses are 95% CI. Univariate parameters with a *p*-value <0.10 were included in multivariate analysis. Bold indicates statistical significance with $p<0.05$

Discussion

FDG-PET is used for patients with colorectal cancer to demonstrate extrahepatic disease and as a consequence it may improve patient selection for surgical resection of the liver metastases. In the present study we analysed whether this selection with FDG-PET would result in an improved outcome in surgically treated patients with CRLM, stratified by the CRS of Fong et al.[10] FDG-PET prior to liver resection did not significantly improved DFS or OS in patients with both low and high CRS in the present series.

The role of FDG-PET in staging CRLM has been evaluated in several large studies. Perhaps the most important clinical impact of FDG-PET is the demonstration of extrahepatic disease and as a consequence the reduction of futile laparotomies, which has been demonstrated in several studies.[14,15,18-21] The magnitude of this on surgical management is questioned by the largest randomised-controlled trial on this subject, which demonstrated that a futile laparotomy was avoided in only 3.8% of patients.[16] The present study could not evaluate whether FDG-PET caused a change in clinical management or whether the number of futile operations was reduced compared to patients without a FDG-PET, because only patients who underwent resection of liver metastases were evaluated.

Besides a change in treatment strategy, FDG-PET might lead to better patient selection and as a consequence improved patient outcome after surgery. To our knowledge, the present data are the first to investigate the benefit of FDG-PET on patient outcome stratified by the CRS. DFS was not different between patients with and without a FDG-PET scan with a low CRS. In patients with high CRS similar results are shown, although there was a trend toward a difference in DFS [14 months (95% CI: 7-21) versus 9 months (95% CI: 8-10), p=0.073]. However, in the multivariate analysis this was not an independent factor.

It has been demonstrated that patients with a high CRS are expected to have a poor tumour biology and, therefore, could potentially have more intra- and extrahepatic disease compared to patients with a low CRS.[10] By means of an FDG-PET these metastases might have been detected, resulting in less disease recurrence, which might explain the trend towards a different DFS. In patients with a low CRS there is a minimal risk of occult metastatic disease and the added value of a FDG-PET is therefore limited, if not absent.[22]

Engledow et al. evaluated the yield of the FDG-PET in an attempt to stratify the use of the FDG-PET in patients with CRLM depending on CRS.[23] The influence on management failed to reach statistical difference between low- and high-CRS patients. Based on this series, the Fong et al. CRS[10] should not be used to rationalise the use of FDG-PET in those patients being investigated for potential resection of CRLM.[23] Schüssler-Fiorenza et al. evaluated whether the CRS correlates with yield of FDG-PET in patients with CRLM.[22] There was a significant association between the CRS and the yield on the FDG-PET-scan and they concluded that patients with a low CRS do not benefit from an FDG-PET.

In the present series, the observation that patients with a high CRS selected by FDG-PET do not have a trend towards OS may partially be explained by the fact that currently excellent local and systemic treatment therapies for recurrent disease are available.[24] Patients in the group without an FDG-PET can undergo adequate treatment for recurrence of cancer, resulting in survival rates as high as patients in whom occult metastases were potentially detected preoperatively. Comparable results were found in a recent randomised-controlled trial, the largest to date on CRLM, which compared perioperative chemotherapy with surgery alone.[25] Although perioperative chemotherapy improved DFS in these patients, the mature OS data of this trial were recently presented and no survival difference was reported after a median follow-up of 7 years.[26]

In the study by Ruers et al. fewer futile laparotomies were performed in the FDG-PET group than in the conventional group, and this also did not translate in a difference in DFS or OS.[14] Some authors, however, have reported an improved OS for patients who underwent an FDG-PET compared to those in whom an FDG-PET was not performed.[27,28] These authors conclude that FDG-PET helped in selecting patients who are appropriate for resection and thus have a more favourable prognosis.[28,29]

A strength of the present study is that it presents data from two tertiary referral centers and tried to correct for bias by stratifying patients according to the CRS. However, this retrospective study from two combined databases also has its limitations, because patients were not randomised to undergo FDG-PET. Moreover, this study only focused on resected patients, information on the number of patients who had a futile laparotomy (open and closed) is lacking. Moreover, the number of patients who were not operated on due to unresectable disease preoperatively is also missing in these analyses.

Conclusion

Preoperative imaging modalities are of paramount importance for liver surgeons to select the right patients for surgery and plan the appropriate surgical strategy for removing all metastatic disease. Especially patients with CRLM and a high CRS have a higher risk of extrahepatic disease and early recurrence. This retrospective study demonstrated no difference in DFS or OS when patients are selected by an FDG-PET-scan in low-CRS patients. Despite a trend towards an improved DFS, we could not demonstrate a benefit of FDG-PET selection in high risk patients, but future prospective studies should focus on this patient category.

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CHAPTER 8

Histopathological evaluation of resected colorectal liver metastases: what should be done?

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Abstract

Background: Histological reporting of liver resections of colorectal liver metastases (CRLM) is limited to confirmation of diagnosis and evaluation of resection margins. A more exhaustive diagnostic reporting might be warranted. Here we critically and systematically review the potentially important histological prognostic factors in CRLM.

Methods: Potential important histological features have been defined, like intrahepatic spread, resection margins and tumour response to neo-adjuvant chemotherapy. Intrahepatic spread (venous, lymphatic, bile duct and perineural invasion) was evaluated in a number of studies.

Results: Meta-analysis demonstrated a clear correlation with 5-year overall survival of portal vein invasion (RR 1.8, 95%-CI 1.3-2.5) and lymphatic invasion (RR 1.7, 95%-CI 1.4-2.0). The impact of hepatic vein invasion and bile duct invasion on outcome is not clear. Perineural invasion was linked to survival in one study. Resection margins is an important prognostic factor, however the extent of negative margins remains controversial. Various studies evaluated tumour response to neo-adjuvant chemotherapy, but different grading systems were used, and definite recommendations cannot be made.

Conclusion: With the high incidence of CRLM and the increase of the number of liver resections, we need well defined prognostic factors, studied in homogenous patient populations to optimise diagnostic work-up. This review identifies several of these factors.

Introduction

Liver metastases are the major cause of death in colorectal cancer patients, with an overall survival in untreated patients of less than 10 months.[1,2] Surgery is the only way to achieve long-term survival, with 5-year survival rates ranging from 40-60%.[3-6] These survival rates are almost the same as those of patients with TNM Stage III colorectal cancer.
Because of improvements in radiological imaging techniques, surgical techniques, perioperative care and the availability of effective systemic therapy, increasing numbers of patients are being selected for resection of their colorectal liver metastases (CRLM). However, there is no clear consensus on the resectability of liver metastases.[1,7-9] Several clinical scoring systems have been developed for patient selection and to predict overall survival (OS) after liver resection, with size, number and the interval between the treatment of the primary tumour and development of CRLM, as important prognostic items.[4,10,11] In addition to the clinical scoring systems, it seems highly probable that molecular and histopathological features of resected CRLM could have potential value in the selection of patients who may benefit from adjuvant systemic treatment. For primary colorectal carcinoma, many prognostic histological factors have been identified and therapeutic decisions concerning adjuvant systemic therapy are made on the basis of these histopathological findings.[12] However, in reporting metastatic lesions usually only confirmation of the malignancy, and the (lack of) involvement of resection margins is mentioned. A more exhaustive diagnostic reporting of the metastases might be warranted. In this article we critically review potentially important prognostic factors for resected CRLM and focus specifically on histopathological features.

Resection margin

The surgical margin of liver metastases is an important prognostic factor. Patients with positive margins usually have a worse outcome.[3,13-15] Although patients with a negative resection margin have an improved outcome, the significance of the width of the negative margins remains controversial. Traditionally, anatomical resection was proposed in liver surgery in order to achieve minimal margins of 10 mm.[16] Dhir et al. conducted a meta-analysis of 18 studies with 4821 patients, to determine whether negative resection margins of ≥10 mm confer a survival advantage over negative resection margins <10mm. The 5-year overall survival rate for the subgroup with margins of ≥10 mm was 46% (95% CI, 44%-48%), as compared to 38% in the subgroup <10mm (95% CI, 36%-40%), suggesting that a margin of 10mm should be pursued. However, owing to anatomical restrictions, these margins cannot always be achieved and might not always be necessary, especially in the era of neo-adjuvant chemotherapy.[9,18] Ayez et al. described similar disease-free and overall survival rates in patients with either R0 or R1 resection treated with neo-adjuvant chemotherapy, suggesting that microscopic tumour remnants after treatment are no longer of major importance, and

that survival after neo-adjuvant chemotherapy is more related to tumour biology than to resection margins.[18] A molecular approach in a limited number of patients (*n*=12) showed that DNA of tumour cells could still be detected at 4 mm from the tumour.[19] Biopsies of surrounding liver tissue at 8, 12 and 16 mm from the tumour border showed no tumour DNA, suggesting that a resection margin >4 millimeters is adequate.

Intrahepatic invasion

Theoretically, metastatic tumour cells can spread within the liver using different pathways. Tumour cells might use preexisting portal and hepatic veins, lymphatic vessels, bile ducts and nerves for dissemination within and outside the liver. Multiple studies investigated the incidence of intrahepatic spread; however, the exact definitions of intrahepatic spread and the methods used to detect it were not described in most articles.[20-29] Only two studies defined the different forms of intrahepatic spread[24,28], of which one also specified the methods used for detection.[28] The study by Sasaki et al. defined portal vein, hepatic vein and bile duct invasion as cancer cells growing in the lumen of a vessel or bile duct branches within the liver.[24] Intrahepatic lymphatic invasion was described as cancer cells in the luminal structure in the portal area, which is lined by endothelial cells. The study by Korita et al. defined lymphatic invasion as single tumour cells or cell clusters visible within vessels that show immunoreactivity for D2-40 monoclonal antibody.[28] Other forms of intrahepatic spread (portal vein, hepatic vein, sinusoidal and bile duct invasion) were not defined in this study.[28] With standard HE staining lymphatic vessels cannot be distinguished from blood vessels (Figure 1A). D2-40 staining of the lymphatic vessels could be helpful in detecting tumour cells within lymphatic vessels (Figure 1b). This staining was used in one study,[28] and, because other studies did not mention their method to visualise lymphatic invasion, it remains unclear how they differentiated between invasion of blood or lymphatic vessels.

Portal vein invasion

Eight studies investigated the incidence of portal vein invasion in colorectal liver metastases (Figure 2).[20-24,26'28'29] These studies included 607 patients in total. The mean incidence of portal vein invasion was 26.2% (range: 10-49%). Four studies (*n*=247) reported data on 5-year OS in patients with and without portal vein invasion.[20,23,24,29] Although the sample sizes of these studies are relatively small, leading to significant heterogeneity, there seems to be a better overall survival in patients without portal vein invasion (RR 1.77, 95%CI 1.26-2.47) (Figure 3a).

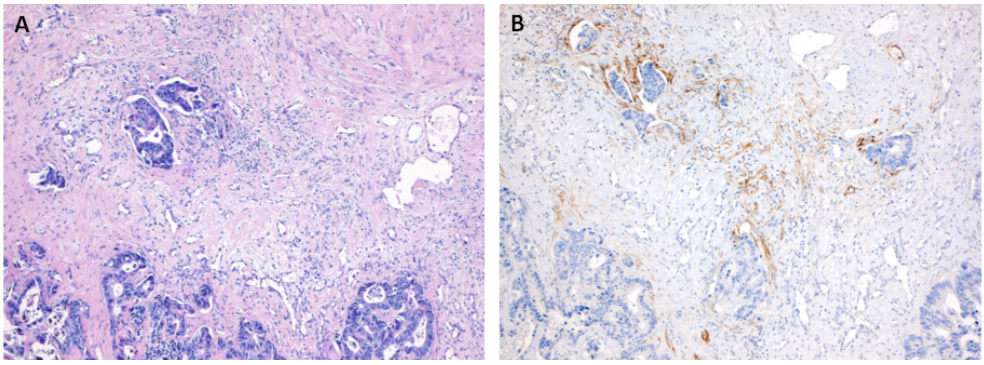

Figure 1A. Haematoxylin and eosin staining at the border of a tumour. Small vessels are present, but differentiation between blood and lymphatic vessels is difficult. **Figure 1B.** Immunohistochemical staining with the D2-40 monoclonal antibody reveals tumour cells within lymphatic vessels.

Hepatic vein invasion

Seven studies investigated the incidence of hepatic vein invasion (Figure 2).[20-24, 26,28] They included 523 patients, 62 of whom had hepatic vein invasion (11.9%, range: 5-24%). Three studies (*n*=192) investigated the impact of hepatic vein invasion on 5-year OS.[20,23,24] Because of the small number of patients, the impact of hepatic vein invasion remains unclear (RR 1.53, 95%CI 0.81-2.89) (Figure 3b).

Lymphatic invasion

Two studies investigated the incidence of lymphatic invasion (Figure 2), with a total number of 170 patients. Lymphatic invasion was found in 12% and 15% of CRLM.[24,28] Both studies showed a negative impact for lymphatic invasion on survival (1.66, 95%CI 1.42-1.95) (Figure 3c).

Bile duct invasion

Nine studies investigated the incidence of bile duct invasion (Figure 2).[21-28] These studies covered 781 patients, 30.2% of whom had bile duct invasion (range: 13-42%). Five studies (*n*=382) reported data on 5-year OS in patients with and without bile duct invasion of the CRLM.[20,23-26] There seems to be no correlation between bile duct invasion of the CRLM and clinical outcome (1.22, 95% CI 0.94-1.58) (Figure 3d).

Perineural invasion

Three studies investigated the incidence of perineural growth in CRLM (Figure 2).[20,21,26] Perineural invasion was found in 40 of 285 patients (14.0%) (range: 12-17%). One study by Yamamato investigated the impact of perineural invasion of colorectal liver metastases on 5-year OS and found a negative impact of perineural invasion.[20]

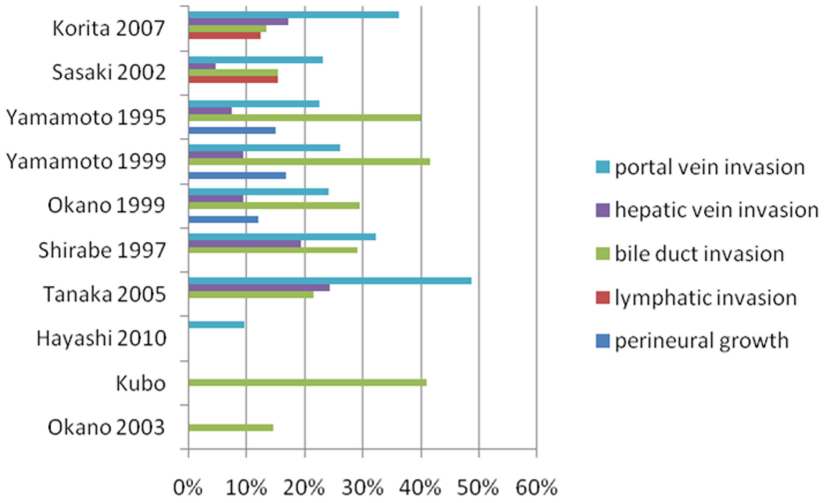

Figure 2. Frequency of different types of intrahepatic spread

Presence of micrometastases

In analogy with primary colorectal tumour, micrometastases may occur in liver metastases. Micrometastases are defined as discrete microscopic cancerous lesions ranging from a single cell to clusters of cells within the liver parenchyma or portal tracts surrounding the dominant macroscopic hepatic tumour. Yokoyama et al. detected micrometastases in 32 of 46 patients using CK20 staining.[30] Patients with micrometastases were reported to have a higher probability of intrahepatic recurrence and poorer survival. They had a 10-year survival rate of 21.9%, versus 64.3% in patients without micrometastases. In the definition used by Yokoyama, there is an overlap between micrometastases and intrahepatic spread.

Presence of fibrous capsule

The presence of a fibrous capsule has been recognised as a favourable prognostic factor in hepatocellular carcinomas.[31] A study by Okano et al. investigated the prognostic value of fibrous capsule in liver metastases of colorectal origin.[32] Fibrotic tissue between the tumour and surrounding liver parenchyma was classified as thick (≥10 layers of collagen bundles) or thin (several layers of collagen bundles). Fibrotic tissue was observed in 61% of patients and was associated with improved survival. Patients with a thick pseudocapsule reached 5-year survival rates of 88%, as compared with 64% in patients with a thin pseudocapsule and 31% in patients without a pseudocapsule. Yamamoto et al. confirmed the prognostic value of a fibrous pseudocapsule after hepatectomy for colorectal metastases.[20] A thick pseudocapsule was associated with 5-year survival rate of 71%, a thin pseudocapsule with 5-year survival rate of 63% and the absence of a pseudocapsule with a 5-year survival rate of only 19%.

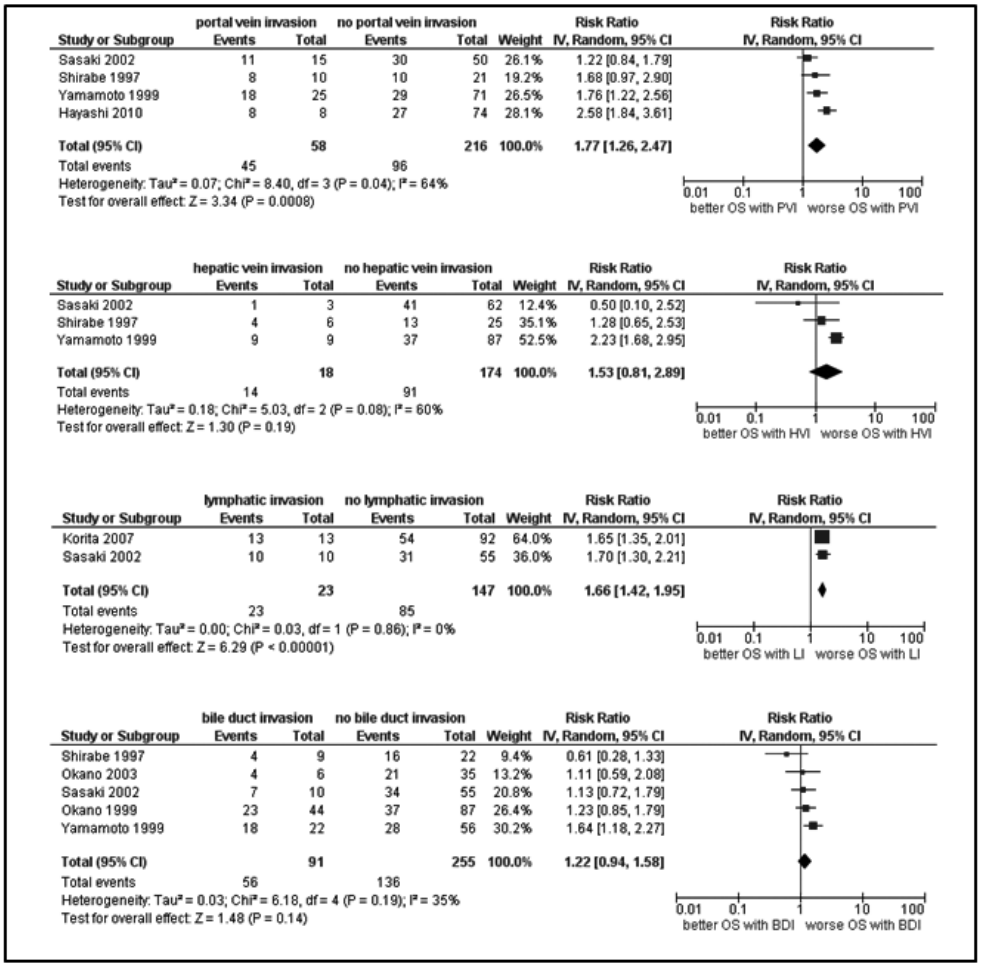

Figure 3. Forest plots for the prognostic value of intrahepatic spread. **A.** Portal vein invasion (PVI). **B.**Hepatic vein invasion (HVI). **C.** Lymphatic invasion (LI). **D.** Bile duct invasion (BDI). CI: confidence interval, OS: overall survival.

Response to neo-adjuvant chemotherapy

Tumour regression grading

Five studies have investigated histological response of liver metastases to preoperative chemotherapy (Table 1).[33-37] All studies showed some effect on survival, but different grading systems were employed to assess pathologic response to chemotherapy. Two studies used complete pathological response versus all other responses, including non-responses.[33,37] In the study by Adam et al. each nodule was sampled for histological examination, one block for each centimeter of diameter of the nodule.[33] Complete pathological response was defined as the absence of any viable tumour cells irrespective of the proportions of necrosis and fibrosis. In the study by Tanaka et al. complete pathological response was defined as the

absence of any viable tumour cells, irrespective of the proportions of necrosis and fibrosis, in the largest cut surface of macroscopically confirmed metastatic tumours, or at sites in resected specimens corresponding to areas where metastases initially were detected in preoperative images.[37] A limitation of those grading systems is the inability to identify partial responders who may also have better survival. In addition, even complete pathological response is sensitive to bias, because it depends on the number of lesions assessed and the interpretation of the pathologist. Other pathologic response grading systems are based on a semi-quantitative analysis of the proportion of viable cancer cells remaining and are therefore subject to variability in interpretation.[34,35] It is impossible to determine the percentage of remaining cancer cells, because there is no data on the baseline percentage of tumour cells prior to chemotherapy. Moreover, liver metastases frequently show necrosis surrounded by adenocarcinoma cells, regardless of neo-adjuvant therapy, and the value of necrosis has not been established. A large area of necrosis will decrease the percentage of remaining cancer cells in most grading systems and does not represent the efficacy of chemotherapy.
The grading system of Rubbia-Brandt et al. seems to be the most accurate, because it takes into account the necrotic areas, fibrotic areas and residual cancer cells.[36] Moreover, for its establishment chemotherapy-naïve tumours were used as a control. Although this seems essential, this is the only study that incorporates these controls. This system is a modified version of the tumour regression scheme of Mandard et al. for esophageal carcinomas.[38] The score identifies five tumour regression grades (TRG) on the basis of the presence of residual tumour cells and the extent of fibrosis. TRG1 corresponds to the absence of tumour cells replaced by abundant fibrosis; TRG2 to rare residual tumour cells scattered throughout abundant fibrosis; TRG3 a greater number of residual tumour cells with a predominant fibrosis; TRG4 to large number of tumour cells predominating over fibrosis; and TRG5 to tumour cells without fibrosis.

Tumour thickness at the tumour-normal interface

Maru et al. measured the tumour thickness at the tumour-normal interface of 103 patients with CRLM resected after preoperative chemotherapy.[39] Recurrence-free survival rates were 70% for patients with a tumour thickness <0.5mm, 51% for patients with a tumour thickness between 0.5mm and 5mm, and 35% for patients with a tumour thickness ≥5mm. A limitation of this study is that the role of tumour thickness in chemotherapy-naïve liver metastases was not investigated. Therefore, it could be that tumour thickness at the tumour-normal interface is a prognostic factor, rather than a predictive factor for response to chemotherapy.

Table 1. Correlation of histological response of colorectal liver metastases after neo-adjuvant systemic therapy with 5-year overall survival

Reference	*n*	Neo-adjuvant chemotherapy	Surgery only	Grading system histological response to chemotherapy	5y OS (%)	*p*-value
Adam *et al.*[33]	767	767	-	Complete pathological response (*n*=29)	76%	0.004
				No complete pathological response (*n*=738)	45%	
Blazer *et al.*[34]	271	271	-	Complete response (no residual cancer cells) (*n*=25)	75%	0.037
				Major response (1%-49% residual cancer cells) (*n*=97)	56%	0.028
				Minor response (>50% residual cancer cells) (*n*=149)	33%	
Chan *et al.*[35]	50	50	-	Strong pathological response (<10% viable tumour cells) (*n*=17)	80%	0.019
				Weak pathological response (>10% viable tumour cells) (*n*=33)	51%	
Rubbia-Brandt *et al.*[36]	181	112	69	Major or complete histological tumour regression (TRG 1+2) (*n*=27)	41%	0.0003
				Partial histological tumour regression (TRG 3) (*n*=36)	38%	
				No histological tumour regression (TRG 4+5) (*n*=49)	9%	0.019
Tanaka *et al.*[37]	63	63	-	Complete pathological response (*n*=23)	69%	0.001
				No complete pathological response (*n*=40)	8%	

OS: overall survival; TRG: tumour regression grade.

Number of lesions to be assessed for chemotherapy response

There is conflicting literature on the histological response to chemotherapy of different liver metastases within one patient. Rubbia-Brandt et al. showed 89% concordance in histological response.[36] However, Tanaka et al. found that, within the same patient, some liver metastases showed a complete response, whereas other metastases did not. Better survival was demonstrated in patients with a pathological complete response in at least one liver metastasis than in patients with no pathological complete responses. The best overall survival was reached in patients with all lesions showing complete responses. Until there are more data on the variation in histological response of multiple liver metastases within a patient, histological sampling of each lesion is recommended to assess the pathological response to chemotherapy.

Discussion

The benefits of liver resection for survival in patients with CRLM are well established; however there still is a challenge in selecting the right patients and preventing recurrence. Macroscopic features of resected metastases, such as size, number and synchronous or metachronous disease are important prognostic factors in many studies. These, together with staging of the primary tumour, are factors in clinical risk scores (CRS), such as that of Fong et al.[4] This CRS is widely used to stratify patients in high-risk and low-risk groups for overall survival.[40,41]

In analogy with primary tumours, histopathological factors such as vascular or perineural invasion and response to chemotherapy, have been investigated in CRLM. Whereas studies in primary colorectal cancer typically consist of large series of patients, in which well-defined histological factors are investigated, pathological research in liver metastases is still in its infancy. Potentially useful factors have been investigated in relatively small, sometimes heterogeneous, groups of patients, but the evaluation of promising factors, such as intrahepatic invasion and tumour regression grade, will require study of larger series, with, for investigation of tumour response to neo-adjuvant chemotherapy, use of well-defined grading systems with chemotherapy-naïve liver metastases as controls.

With the high frequency of CRLM and the increasing number of liver resections, there is a need for well-defined prognostic histopathological factors. Prospective studies of populations of patients with CRLM are warranted to evaluate prognostic and/or predictive factors such as histopathological features and (novel) biomarkers, in order to assist treatment decisions.

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CHAPTER 9

Lymphatic invasion is an independent adverse prognostic factor in patients with colorectal liver metastasis

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Abstract

Background: For a selection of patients with colorectal liver metastases (CRLM), liver resection is a curative option. In order to predict long-term survival clinico-pathologic risk scores have been developed, but little is known about histologic factors and their prognostic value for disease-free and overall survival. The objective of the present study was to assess possible prognostic histologic factors in patients with solitary CRLM treated with liver resection who did not receive neo-adjuvant treatment.

Methods: Patients with solitary CRLM who underwent liver resection between 1992 and 2011 were evaluated for clinical prognostic factors. Histologic analyses on tumour-thickness at the tumour normal interface, presence of a fibrotic capsule, intrahepatic vascular invasion, lymphatic invasion, or bile duct invasion and perineural growth were performed, using immunohistochemistry.

Results: A total of 124 patients were analysed with a median follow-up of 41 months (range: 1-232 months). There was no association between histologic factors and disease-free survival in multivariate analysis. In multivariate analysis, intrahepatic lymphatic invasion was associated with a decreased overall survival (41.9 months versus 61.0 months) (p=0.041), especially in combination with vascular invasion (n= 15) (28.1 months versus 62.2 months; p<0.0001). In addition, size over 50mm (29.2 months versus 65.9 months; p=0.004) and interval less than 12 months between resection of the primary tumour and diagnosis of liver metastasis (49.0 months versus 91.5 months: p= 0.019) were also independent adverse prognostic factors.

Conclusion: Intrahepatic lymphatic invasion, especially in combination with vascular invasion, is an important adverse prognostic factor for overall survival in patients with solitary CRLM after liver resection.

Introduction

Colorectal cancer is one of the leading causes of cancer death worldwide as a result of its considerable risk of development of metastases.[1] When metastatic disease is confined to the liver, partial liver resection is the only curative therapeutic option, with 5-year overall survival percentages (OS) between 20 and 60%, depending on patient and tumour characteristics.[2-4] In order to explain these varying survival rates, different clinicopathologic risk scores have been developed. In many of these risk scores, nodal status of the primary tumour, size and number of the colorectal liver metastases (CRLM), disease-free interval from treatment of the primary until detection of the CRLM and preoperative level of carcinoembryonic antigen (CEA) are combined to predict long-term survival.[5-9] These scoring systems are relevant with respect to prediction of survival, but to our knowledge, have not been used for risk stratification in controversial areas such as the administration of neo-adjuvant or adjuvant systemic therapy or surveillance.

In primary colorectal cancer histologic factors such as extramural venous invasion, perineural growth, lymphatic invasion, angioinvasion and diffuse growth pattern have been associated with poorer survival outcomes.[10,11] Extramural venous invasion in particular is considered a poor prognostic factor, and as a result, patients with extramural venous invasion in stage II colon cancer are considered candidates for adjuvant systemic treatment.[12] Very little is known about the impact of histologic features of colorectal liver metastases on OS, as described in a recent review.[13]

Vascular invasion, bile duct invasion, or lymphatic invasion by tumour cells in CRLM have all been suggested as prognostic factors for long-term survival.[5,14-23] Perineural growth, the presence of a fibrous capsule, and tumour thickness at the tumour-normal interface have also been linked to survival in patients with CRLM.[14,15,19,24-26] Variations in definitions and selection of patients have limited the impact of these studies. Furthermore, none of these previous studies has evaluated multiple histologic factors of the liver resection specimens, in combination with established risk scores in a homogenous group of patients. Most studies included patients who underwent neo-adjuvant therapy as well as chemotherapy-naïve patients, patients with multiple liver metastases, or patients with extrahepatic disease.[5,14-21,23,24]

The results of these previous studies might be biased because of the known changes in histologic features observed in liver metastases after systemic therapy, and the possible heterogeneous nature of multiple metastases.[27-30]

The objective of the current study was to assess possible prognostic histologic factors for long-term survival in patients with solitary colorectal liver metastasis who underwent a complete liver resection (R0) without neo-adjuvant systemic therapy.

Materials and methods

Patients

Patients were identified who underwent complete liver resection (R0) for a solitary CRLM between 1992 and 2011 in a tertiary referral hospital. R0 resections were defined as liver resections with clear resection margins in patients that did not have evidence of disease in any other locations. Demographics and clinico-pathologic factors with regard to the primary tumour, as well as the liver metastasis, were collected per patient. Special attention was given to the four different items from the clinical risk score according to Fong et al.: nodal status of the primary tumour; preoperative CEA level and size of the metastasis, and interval between resection of the primary tumour and diagnosis of CRLM.[9] It is unknown whether systemic treatment influences the presence of certain histopathologic factors and therefore patients who were treated with neo-adjuvant systemic therapy were excluded from the current study. Patients who died from post-operative complications, defined as within 30 days after liver resection, were also excluded. Patients underwent follow-up according to our current Dutch follow-up guidelines, with regular outpatient visits, CEA testing and computed tomographic scans of chest and abdomen.

Histopathology

R0 liver resection specimens with a solitary CRLM were selected from the archive. Routine work up consisted of sampling of macroscopically normal liver tissue, invasive front of the metastasis, and additional tumour blocks, depending on the size of metastasis. Slide revision was performed independently by two investigators (JdR, NK). Discrepancies were resolved by simultaneous re-examination of the slides by both investigators using a two-headed microscope. In case of discrepancy, the senior pathologist (IN) made the final call. Tumour thickness at the tumour-normal interface was determined in routine slides. Tumour-normal interface was defined as the interface between tumour and normal liver tissue, as described by Maru et al. and validated by others.[26,31,32] In all tumours, tumour thickness was measured with a ruler at multiple foci, and maximum tumour thickness was used and defined as uninterrupted layers of tumour cells without admixed fibrotic stroma, acellular mucin or non-neoplastic liver parenchyma. The median tumour thickness at tumour-normal interface was used to divide the patient group in a group with a larger and a smaller layer of vital tumour cells (Figure 1).

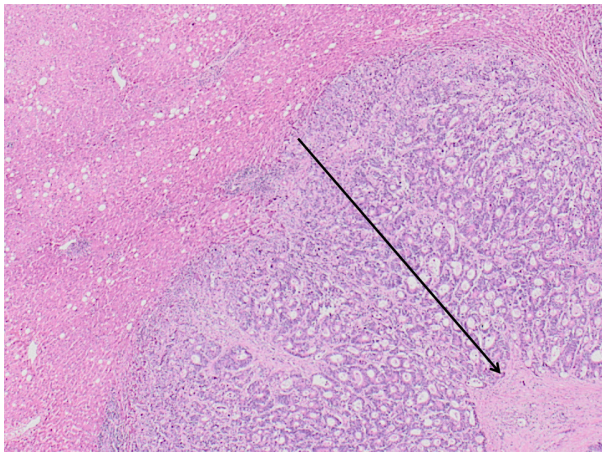


Figure 1. Tumour thickness at the tumour-normal interface; the arrow indicates correct measurement with an uninterrupted layer of tumour cells. Original magnification x 10.

The presence of a fibrotic capsule around the metastasis was evaluated in routine slides. The fibrous tissue between tumours and liver parenchyma was classified as absent (no fibrous tissue observed) or present (the tumour was separated from the liver parenchyma by several layers of collagen bundles in histological sections) (Figure 2).

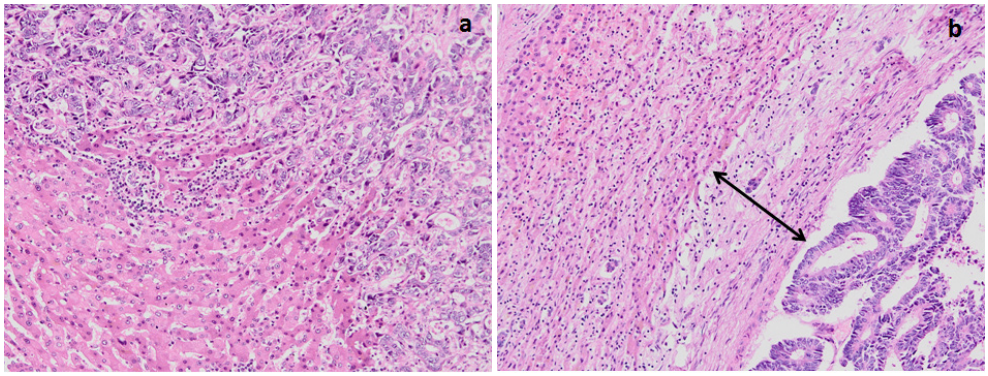


Figure 2a. Colorectal liver metastasis without a fibrous capsule. Original magnification x 20. **Figure 2b.** Colorectal liver metastasis with a fibrous capsule (*arrow*). Original magnification x 20.

Immunohistochemistry and scoring methods

Immunohistochemistry was performed as previously described.[33] Antibodies, clones, dilution and retrieval methods are summarised in Table 1.

Perineural growth was defined as a nerve, identified by S-100 staining, being surrounded by tumour cells for at least three quarters of the circumference and was scored as being present or absent (Figure 3a).

Lymphatic invasion was defined as single tumour cells or cell clusters visible within vessels that show immunoreactivity for D2-40 but not for CD31.
Lymphatic invasion was scored as being present or absent (Figure 3b). Vascular invasion was defined as single tumour cells or cell clusters visible within vessels that show immunoreactivity for CD31 but not for D2-40. It was scored as being present or absent (Figure 3c). Bile duct invasion was defined as single tumour cells or cell clusters (CK7 negative) visible within bile ducts which show immunoreactivity for CK7. It was also scored as being present or absent (Figure 3d).

Table 1. Antibodies, clones, dilution and retrieval methods used in the current study to evaluate intrahepatic vascular invasion (CD-31), lymphatic invasion (D2-40), bile duct invasion (CK-7) and perineural growth (S-100).

Antibody	Clone	Dilution	Ab-retrieval	Source
CD-31	M0823	1:40	EDTA	Dako, Denmark
D2-40	CM266C	1:50	EDTA	Biocare Medical, Belgium
CK-7	MU255-UC	1:800	Pronase	Klinipath, Netherlands
S-100	Z0311	1:2000	EDTA	Dako, Denmark

Outcome

Primary outcomes were disease-free (DFS) and overall survival (OS). DFS was defined as the interval in months between liver resection and disease recurrence, death or last follow-up. OS was defined as the interval in months between liver resection and death or date of last follow-up.

Statistical analyses

Pearson's Chi square test was used to calculate correlations between the various histologic features. Survival curves were estimated by the Kaplan-Meier method and compared by log-rank testing. Multivariate analysis was performed using Cox proportional hazard model, and variables were included that were associated with survival in univariate analysis with a p-value < 0.10. The SPSS statistical package, version 18.0 (SPSS, Inc., Chicago, Illinois, USA) was used for all statistical analyses. A p-value of < 0.05 was considered statistically significant.

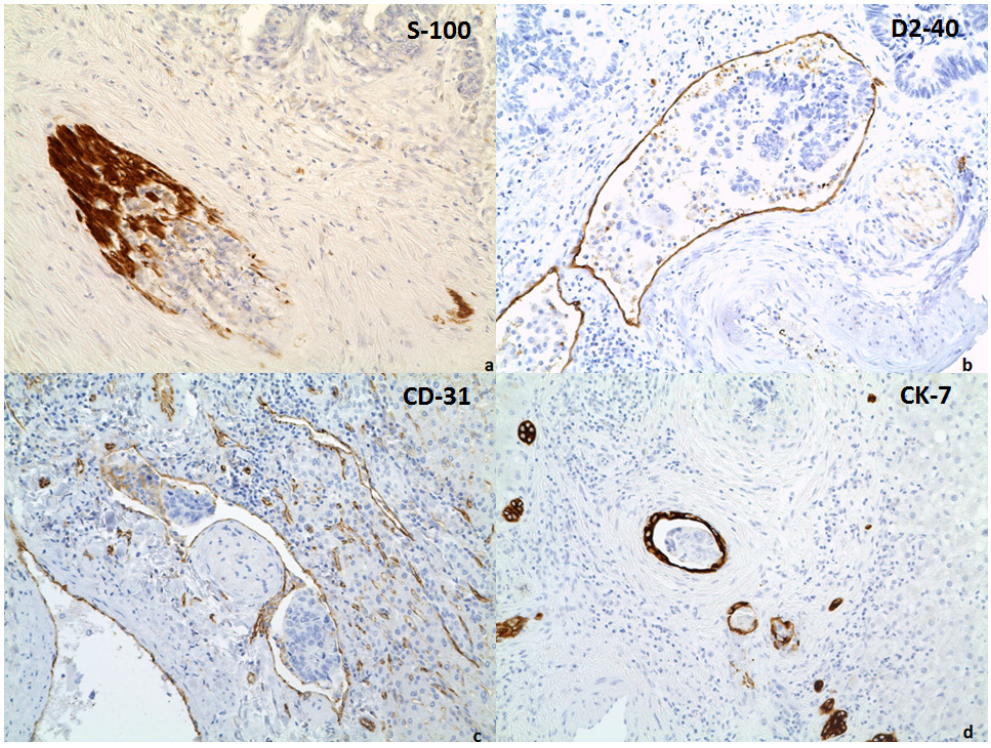


Figure 3. Different forms of intrahepatic invasion by tumour cells. **a:** Perineural growth showing S-100 reactivity. **b:** Lymphatic invasion showing D2-40 reactivity. **c:** Vascular invasion showing CD-31 reactivity. **d:** Bile duct invasion showing CK-7 reactivity. Original magnification x 20.

Results

Patients

Between January 1992 and March 2011, a total of 383 patients underwent liver resection for metastatic disease. After excluding patients with multiple metastases, 135 patients remained who were surgically treated (R0) for solitary CRLM. Eleven patients were excluded because they received neo-adjuvant chemotherapy (*n*=5), were lost to follow-up (*n*=2), or died within 30 days after liver resection (*n*=4). A total of 124 patients were eligible to be included in the current study, 76 men (61.3%) and 48 women (38.7%). Median age at time of resection was 64 years (range: 40-80 years). Liver metastases were detected at a median of 8.8 months (range: 0-82 months) after resection of the primary tumour. Median size of the metastasis was 35 mm (range: 10-130mm). Median follow-up was 41 months (range: 1-232 months). In the complete study population, median DFS was 28 months (range: 1-228 months) with a median OS of 57 months (range: 1-232 months) and a 5-year survival of 48.1%.

Histopathological tumour features

Fibrous capsule and tumour thickness

In 34.4% of patients (*n*=43) the liver metastasis was surrounded by a fibrous capsule. Presence of a fibrous capsule was not associated with DFS, but it was associated with an improved OS of 109.3 months, versus 56.7 months in patients without a fibrous capsule (*p*=0.037). In multivariate analysis, presence of a fibrous capsule was not an independent risk factor for OS (Tables 2 and 3). Tumour thickness at tumour-normal interface varied between 0.1 and 7.2 mm, with a median of 3 mm, and was not correlated with the size of the liver metastasis (*p*=0.213). Although there was a significant association of increased thickness with decreased outcome (both DFS and OS) in univariate analysis, it was no longer significant in multivariate analysis (Tables 2 and 3).

Intrahepatic spread

Frequency of different forms of intrahepatic invasion varied; perineural growth (*n*=11; 8.9 %) and bile duct invasion (*n*=11; 8.8%) were both relatively uncommon, whereas vascular and lymphatic invasion were seen more frequently (*n*=46; 37.1%, respectively *n*=33; 26.6%). In univariate analysis, the presence of bile duct invasion was associated with improved OS (76.7 versus 55.9 months; *p*=0.048), but this was not the case in multivariate analysis (*p*=0.094). Presence of intrahepatic lymphatic invasion was correlated with a decreased median OS (41.9 versus 62.2 months, *p*=0.013), which remained significant in multivariate analysis (*p*=0.041) (Figure 4a).

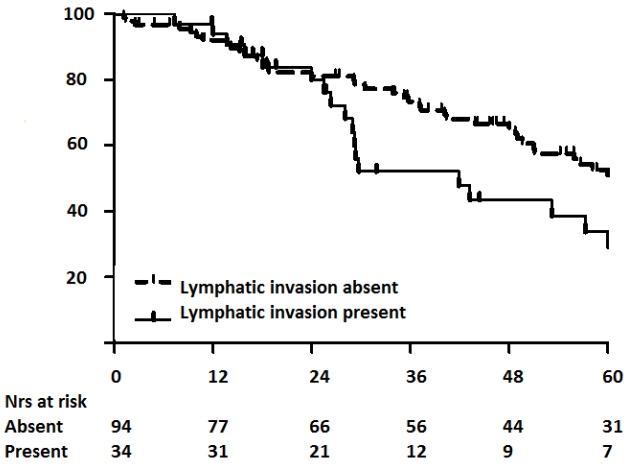
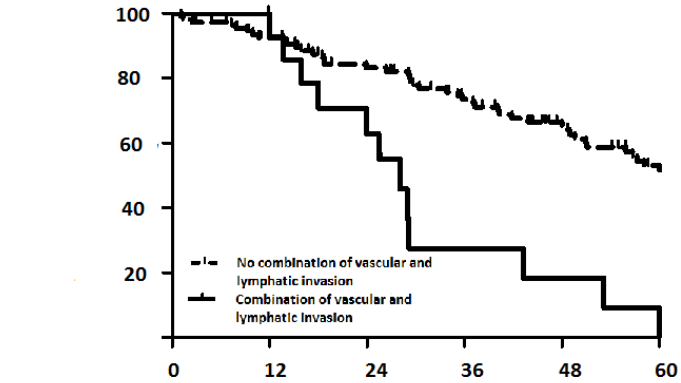


Figure 4a. Overall survival in months after liver resection for solitary colorectal liver metastases in patients with and without intrahepatic lymphatic invasion (*p*=0.013). Survival in months on the X-axis and survival in percentages on the Y-axis

In the current study no correlation between different forms of intrahepatic spread or between any of the histologic features and the various items of the clinical risk score was observed. However, there was a correlation between presence of a fibrous capsule and absence of intrahepatic vascular invasion (p=0.014) and between presence of a fibrous capsule and presence of intrahepatic bile duct invasion (p=0.013).

In 15 patients, a combination of intrahepatic lymphatic invasion and intrahepatic vascular invasion was present, and this combination was associated with a decreased OS (median 28.1versus 62.2 months) in univariate and multivariate analyses (p<0.0001) (Figure 4b).



Nrs at risk						
No Combination	109	94	79	65	50	37
Combination	15	14	8	3	2	1

Figure 4B. Overall survival in months after liver resection for solitary colorectal liver metastases in patients with the combination of intrahepatic lymphatic and vascular invasion and without this combination (p<0.0001). Survival in months on the X-axis and survival in percentages on the Y-axis

Table 2. Relation of clinical and histologic factors with disease-free survival after liver resection in patients with solitary liver metastasis.

		n	%	Median DFS	*p*-value UV analysis	*p*-value MV analysis
Size	≤50mm	93	75%	50.1	**0.002****	**0.020****
	>50mm	31	25%	14.5		
CEA	≤200ng/ml	121	97.6%	27.5	0.508	-
	>200ng/ml	3	2.4%	40.6		
DFI (months)	≤12	72	58.1%	27.8	0.232	-
	>12	52	41.9%	25.4		
Nodal state primary	N0	54	43.5%	35.7	0.446	
	N+	70	56.5%	27.5		-
Adjuvant Tx	No	106	85.5%	20.2	**0.013****	**0.025****
	Yes	18	14.5%	>50		
Tumour thickness at TNI	≤3mm	60	48.4%	>51	**0.023****	0.118
	>3mm	64	51.6%	19.4		
Fibrous capsule	Present	43	34.4%	27.8	0.468	-
	Absent	81	65.6%	25.8		
Perineural growth	Present	11	8.9%	50.2	0.539	-
	Absent	113	91.1%	27.5		
Vascular invasion	Present	46	37.1%	18.0	0.055	0.287
	Absent	78	62.9%	40.8		
Lymphatic invasion	Present	33	26.6%	19.4	0.280	-
	Absent	91	73.4%	29.2		
Bile duct invasion	Present	11	8.8%	27.8	0.624	-
	Absent	113	91.2%	27.5		

DFS: disease-free survival, *UV*: univariate analysis, *MV*: multivariate analysis, *CEA*: carcinoembryonic antigen, *DFI*: disease-free interval between treatment of the primary tumour and detection of the colorectal liver metastases, *TNI*: tumour-normal interface.
***p*-value of < 0.05 was considered statistically significant

Table 3. Relation of clinical and histologic factors with overall survival after liver resection in patients with solitary colorectal liver metastasis

		n	%	Median OS	*p*-value UV analysis	*p*-value MV analysis
Size	≤50mm	93	75%	65.9	**0.050****	**0.004****
	>50mm	31	25%	29.2		
CEA	≤200ng/ml	121	97.6%	57.3	0.912	-
	>200ng/ml	3	2.4%	28.9		
DFI (months)	≤12	72	58.1%	49.0	0.059	**0.019****
	>12	52	41.9%	91.5		
Nodal state primary	N0	54	43.5%	61.0	0.231	-
	N+	70	56.5%	44.6		
Adjuvant Tx	No	106	85.5%	57.2	0.955	-
	Yes	18	14.5%	29.2		
Tumour thickness at TNI	≤3mm	60	48.4%	95.3	**0.043****	0.068
	>3mm	64	51.6%	48.8		
Fibrous capsule	Present	43	34.4%	109.3	**0.037****	0.240
	Absent	81	65.6%	56.7		
Perineural growth	Present	11	8.9%	109.3	0.652	-
	Absent	113	91.1%	55.9		
Vascular invasion	Present	46	37.1%	48.8	0.483	-
	Absent	78	62.9%	58.2		
Lymphatic invasion	Present	33	26.6%	41.9	**0.013****	**0.041****
	Absent	91	73.4%	62.2		
Bile duct invasion	Present	11	8.8%	76.7	**0.048****	0.094
	Absent	113	91.2%	55.9		

OS: overall survival, *UV*: univariate, *MV:* multivariate, *CEA*: carcinoembryonic antigen, *DFI*: disease-free interval between treatment of the primary tumour and detection of the liver metastases, *TNI:* tumour-normal interface * *p-value of <0.05 was considered statistically significant

Discussion

The current study describes the association between multiple histologic features in combination with clinical factors and survival in 124 patients who underwent liver resection for CRLM. An homogenous group of patients was evaluated because all patients underwent a complete resection (R0), for a solitary metastasis without neo-adjuvant systemic treatment. The only significant histologic factor associated with decreased survival in multivariate analysis was the presence of intrahepatic lymphatic invasion, especially in combination with intrahepatic vascular invasion.

Other authors also described lymphatic invasion as a negative predictor for survival.[13,18,20] In the current study, we observed a relative high frequency of lymphatic invasion (26.6%) compared to earlier studies (12%-15%).[18,20] This might be due to the use of immunohistochemistry, which is supported by a recently published study with the same methodology and a similar frequency of lymphatic invasion (29%).[18,20,34-36] Presence of lymphatic invasion has been associated with spread to hepatic lymph nodes, which often leads to incurable disease.[20,37] In the current study, the worse prognosis was demonstrated in patients with a combination of vascular and lymphatic invasion. This unfavourable combination has been observed before and might reflect a tumour with aggressive behavior.[23]

Another interesting finding from the current study was that the median tumour thickness at tumour-normal interface in patients who were not treated with neo-adjuvant systemic therapy was 3.0 mm. This was only slightly higher than the tumour thickness of 2.8mm described in patients treated with neo-adjuvant chemotherapy.[26] This raises the question whether tumour thickness at tumour-normal interface reflects chemotherapy response or tumour biology; this would be an interesting subject for further research.

A major strength of the present study is the inclusion of patients with solitary CRLM only, who were operated with complete margins (R0) to create a homogenous group of patients. Previous studies on histologic prognostic factors included patients with multiple CRLM and R1 resections as well, which might lead to significant bias of the results.[18,20,36] First, heterogeneity of histologic features between the different liver metastases might exist and could lead to bias studying prognostic factors for survival. Second, patients who undergo R1 resection usually have a higher risk on local recurrences and have an impaired survival.[38,39] Third, patients with multiple metastases have a significantly decreased survival, and number of metastases is the most important factor in the Fong classification for survival.[9] By excluding these potential biases in the present study, the assessment of the prognostic histologic factors is more reliable.

Another strength of the present study is that this homogenous group of patients with solitary metastasis were not treated with neo-adjuvant systemic therapy. In recent studies, patients with and without neo-adjuvant systemic therapy were mixed, and conclusions were drawn from a population highly susceptible to bias.[25,36,40] Neo-adjuvant systemic therapies have a significant impact on tumour histology, and even prognostic factors such as resection margins might be less important.[27,28,41] Because the detection of histologic prognostic factors in metastatic disease is still in its infancy and the effects of neo-adjuvant systemic therapy on lymphatic invasion are unknown, a study with a homogeneous population should be a first step. However, there seems to be an increasing preference to utilise neo-adjuvant systemic therapy for high risk patients, despite a lack of convincing evidence on survival benefit in patients with limited metastases.[42-44] Therefore, a limitation of the present study is

that the impact of lymphatic invasion on survival has to be confirmed in patients treated with neo-adjuvant systemic therapy. In the total group of patients treated in our institution only 5 patients (3.8%) with solitary metastasis were treated with neo-adjuvant chemotherapy, which made it impossible to compare, but this should be the goal for future research.
In conclusion, intrahepatic lymphatic invasion, based on immunohistochemical detection of lymphatic vessels, is an adverse prognostic factor for OS in patients with a solitary CRLM. Therefore, we recommend evaluating the presence or absence of intrahepatic lymphatic and vascular invasion in the histologic assessment of CRLM. Future research is needed to determine whether adjuvant treatment strategies should be based on these adverse prognostic histological factors.

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CHAPTER 10

Summary of this thesis and future perspectives

Summary of this thesis

Incidence of liver metastases and liver resection

Many newly diagnosed cancer patients present with liver metastases and even more patients develop liver metastases during the course of their disease. Knowledge about the origin of liver metastases is important, especially in those patients who present with metastases and where a primary tumour is not (yet) diagnosed.

In ***chapter 2*** more than 23,000 patients with histological confirmed liver metastases were analyzed during a 10- year period (2001-2010). Data were collected from the PALGA database (a nation-wide network and registry of cyto- and histopathology in the Netherlands), and demographics and primary tumour (sub)types were evaluated. Colorectal carcinoma (CRC) was the most common primary tumour location in patients with liver metastases (35%). This percentage might even be an underestimation because liver biopsies are not always performed in CRC patients with suspicious liver lesions, and (systemic) therapies are often started without histological confirmation of metastatic disease.

Liver metastases were more observed in men (53%), with primary tumour locations mainly in the lung (squamous cell carcinoma) or in the colorectum. The majority of patients with liver metastases were older than 50 years (90.2%), although liver metastases from breast cancer and gynecological cancers (squamous cell carcinoma and neuroendocrine carcinoma) were relatively more diagnosed in women younger than 50 years. In older men (>70 years) liver metastases from the urological tract and squamous cell lung carcinoma were more common.

This large overview of the origins of liver metastases, with regard to tumour types, age and gender, forms a basis for future research, and may be used for the development of diagnostic strategies.

The vast majority of the 23,000 patients, described in ***chapter 2***, underwent liver biopsy only, while just over 3,900 patients underwent a liver resection. ***Chapter 3*** describes all patients who underwent some form of liver resection for metastatic disease in the Netherlands between 2001 and 2010. As expected liver resection was most often performed in patients with colorectal liver metastases (CRLM) (88% of the patients who underwent liver surgery). During the study period, a significant increase of liver resections for CRLM was observed. Part of the increase can be explained by the increasing incidence of primary CRC and as a result more patients with CRLM. Additional explanations can be found in the fact that the indications for liver surgery seem to expand. An increase in patients' age at the time of liver resection, as well as an increase in patients with multiple liver metastases point in this direction.

Non-colorectal liver metastases

The data from ***chapter 2*** showed that almost half of the (histological confirmed) liver metastases originated from a non-colorectal primary tumour. The most common primary malignancies in this patient group were pancreatic cancer, lung cancer, breast cancer and melanoma. Despite the fact that almost half of the patients were diagnosed with non-colorectal liver metastases (non-CRLM), the number of patients that undergo liver surgery for non-CRLM was low, and did not increase during the last decade, as described in ***chapter 3***. Several factors might be responsible for this low amount, such as: the lack of adequate follow-up to discover liver metastases in an early phase, a low number of patients with resectable liver metastases, and lack of evidence that liver surgery is improving outcome in patients with non-CRLM. Nevertheless, a small number of patients with non-CRLM did undergo liver surgery aiming to improve survival.

In ***chapter 4*** all patients with breast cancer liver metastases who underwent liver resection in the Netherlands between 1994 and 2010 (*n*=32) were evaluated. In this highly selected group of patients a median survival of 55 months was found. Factors associated with improved survival were estrogen-receptor-positivity of the primary tumour, solitary metastasis and unilobar distribution.

Chapter 5 describes all patients in the Netherlands between 1994 and 2010 with metastatic melanoma, who underwent liver resection (*n*=32). In this, again, highly selected group of patients, median survival was 29 months. These results are similar to previous, generally single center, international studies and suggest that surgery seems to be associated with improved survival in this highly selected group of patients with non-CRLM.[1-6] Factors associated with improved survival in patients with metastatic melanoma were solitary liver metastasis, unilobar distribution and minor liver resection.

The challenge in patients with non-CRLM is to select those patients who would benefit from liver resection. Factors associated with improved survival have been described, but vary between the reports. For breast cancer liver metastases estrogen receptor status [1,7,8], number of liver metastases [7,8], and free resection margins[9,10] were most often identified as prognostic factors for survival. In patients with metastatic melanoma free resection margins [5,6,11,12], the number of liver metastases [4,6], and the length of the disease-free interval between treatment of the primary melanoma and diagnosis of the liver metastases [4,5,12,13] were the most described factors associated with survival. However, these prognostic factors have been derived from very small patient cohorts, which may very well lead to a high risk of bias. Therefore, these factors can be taken into account in individual cases, but they should not be used to exclude patients from liver surgery.

Colorectal liver metastases

Almost 40% of all CRC patients develop CRLM and only few undergo liver surgery, although the number of liver resections significantly increased in recent years. In ***chapter 3,*** it was estimated that approximately 20% of patients with CRLM underwent liver resection in the Netherlands, which is in line with international data.[14,15] Part of the problem is the assessment of resectability of liver metastases, and that not all patients with liver metastases are being referred to liver surgeons to evaluate potential surgical treatment options. In ***chapter 6*** fifty-six computed tomography (CT) scans of patients with CRLM, who were treated with systemic therapy (without surgery) in two Dutch multicenter randomised clinical trials, were retrospectively evaluated by three independent, experienced, liver surgeons. In 16 patients (29%) there was disagreement between these surgeons whether the CRLM were resectable or un-resectable. Two previous studies also demonstrated that decision-making in patients with CRLM is highly variable, even among experienced liver surgeons.[16,17] Both studies described disagreement between liver surgeons in assessing resectability of the CRLM in almost half of the cases[16,17] This highlights the heterogeneous nature of oncological liver surgery, where the decision-making process is influenced by the individual experience of the treating doctor (colorectal surgeon, liver surgeon or medical oncologist) and by the availability of various treatment options (such as induction systemic therapy, two-stage liver resection, portal vein embolisation (PVE) and various ablative techniques). The extent of treatment options for patients with CRLM is fueling the needs for multidisciplinary team approaches.

Another part of the study in ***chapter 6*** was comparing long term results between patients who underwent surgery or systemic treatment for CRLM. Patients who were treated with systemic therapy for CRLM and were retrospectively considered candidates for surgery by all three liver surgeons after reviewing the CT scans where identified. These 36 patients were case-matched (for gender, age, and the clinical risk factors according to Fong et al.[18]) with comparable patients who underwent liver resection. Patients who underwent liver surgery had a significantly better overall survival (OS) compared to patients who were treated only with systemic therapy (56 versus 26.5 months). Liver resection should therefore remain the 'gold standard treatment' for patients with CRLM, and should always be aimed for.

Prognostic factors

In ***chapter 7*** the value of fluorine-18-deoxyglucose positron emission tomography (FDG-PET) scan as a tool in patient selection for liver surgery was investigated. Survival was assessed in two patient groups with CRLM who underwent pre-operative FDG-PET (*n*= 206) and who did not underwent pre-operative FDG-PET scan (*n= 407*). The results showed that pre-operative FDG-PET scan did not have an additional value in selecting patients for liver surgery, since patients selected with pre-operative FDG-PET scan did not have an

improvement in disease-free (median 17 versus 14 months) or overall survival (median 64 versus 54 months). A recent clinical trial by Moulton et al. evaluated the changes in treatment of CRLM patients scheduled for surgery after a pre-operative FDG-PET scan.[19] They described a change in treatment plan in only 2.7% of the patients, and as a result, routine FDG-PET scan is not recommended in the standard pre-operative work-up in patients with CRLM.

Prognosis of CRC patients after liver metastasectomy improved during the last decade with 5-year overall survival rates above 50%.[20] Nevertheless, the quest for new prognostic factors continues, because, unfortunately, these high survival rates do not count for every CRLM patient. Some patients suffer from early recurrences, leading to inferior survival rates.[20]
In ***chapter 8*** a study of the literature was performed for histopathological factors that might influence survival after resection of CRLM, such as intrahepatic spread, resection margins, and tumour response to neo-adjuvant systemic therapy. Meta-analyses demonstrated a correlation between OS and portal vein and lymphatic invasion, as well as resection margin. However, most studies were performed in heterogeneous patient populations. Therefore, in ***chapter 9***, patients with solitary CRLM, without neo-adjuvant systemic treatment, and with sufficient follow up were retrospectively selected. A total of 124 liver resection specimens were re-examined by two independent observers for relevant histological factors. These histological factors were: tumour-thickness at tumour normal interface and presence of a tumour capsule that were examined in hematoxyline-eosine (HE) stained slides, intrahepatic vascular, lymphatic or angioinvasion, and perineural growth which were identified with immunohistochemistry. In addition to these histopathological factors, Fongs' clinical risk factors were collected (e.g. size of the metastasis, CEA-level, interval between treatment of the primary tumour and detection of liver metastasis, and positive nodal status of the primary tumour).[18] Intrahepatic lymphatic invasion by tumour cells was the only independent adverse histopathological prognostic factor in patients with solitary CRLM, especially in combination with intrahepatic vascular invasion, which may be an expression of aggressive tumour behavior. The value of lymphatic invasion as a prognostic factor needs further research in patients with neo-adjuvant systemic therapy and patients with multiple CRLM.

Future perspectives

In 2014 a nation-wide screening program for CRC was introduced in the Netherlands, for early detection and prevention of CRC. The identification of asymptomatic patients with early stage CRC will hopefully result in a decreased number of patients with CRLM and decreased need for liver surgery. On the other hand, as a result of expanding indications, it can be expected that the increase in the number of liver resections will continue. In this thesis it was demonstrated that, for example, older age seems to be no longer a contraindication for liver surgery, which is supported by other studies.[21,22] Comorbidity and clinical condition remain most important in patient selection for major resection but in liver surgery, future liver remnant has become the most important factor. Methods to increase this remnant liver are portal vein embolisation (PVE) and portal vein ligation (PVL). By inducing liver hypertrophy in the non-embolised liver segments, the volume of future remnant liver is usually increased. After portal ligation or embolisation patients have to wait for several weeks for liver hypertrophy to occur, but in the meantime progression of liver metastases (in the non-embolised segments) might also be induced. A new technique that deals with this potential problem is Associating Liver Partion and PVL for Staged hepatectomy (ALPPS). At first, the liver parenchyma is transected along the intended line of resection and the future remnant liver is cleared by partial resection of all tumour tissue (in case of bilobar disease). A portal ligation to the lobe that will be removed is added. After a waiting period of 1-2 weeks the second step is performed in which the deportalized liver is removed. A greater degree of growth of future remnant liver was observed after ALLPS compared to traditional methods (PVI/PVL) and less time was needed for the liver hypertrophy to occur.[23] ALPPS seems a promising technique, however, a high morbidity, mortality, and increased early recurrences of liver metastases have been reported after ALPPS.[24] A randomised clinical trial comparing ALPPS and two-stage liver resection is currently ongoing in Austria (NCT02758977) and will evaluate the clinical effect of both techniques.

Currently, liver resection in CRLM patients is only performed when with a complete resection (R0) can be achieved. This concept might need adjustment since Ayez et al. described similar long-term results in CRLM patients with complete resection (R0) or microscopic incomplete resection (R1) who were treated with neo-adjuvant systemic therapy.[25] Other patients with advanced CRLM have such a good response after neo-adjuvant systemic therapy that lesions disappear and only visible liver lesions are removed.[26] These patients can have long-term survival and these findings could rise the question if surgical treatment on top of systemic therapy provides any survival benefit for patients with multiple and un-resectable colorectal metastases (liver and other metastatic locations). The ORCHESTRA trial (NCT01792934) is designed for those patients with un-resectable colorectal metastases and randomises

between maximal debulking surgery and continuing systemic therapy. The results of this study have to be awaited, but could potentially lead to debulking surgery as a treatment modality for un-resectable stage IV CRC patients.

In this thesis patients who received neo-adjuvant systemic therapy were excluded from various studies, because it was intended to create and study a homogeneous group of patients. Neo-adjuvant systemic therapy might potentially improve survival, but could also influence prognostic factors for survival after liver surgery. The role of peri-operative systemic therapy in primary resectable CRLM patients was recently reported by Nordlinger et al., and demonstrated no survival benefit after 7-years of follow-up.[27,28] In their study, patients were not stratified by clinical risk score, and it may be hypothesized that only patients with a 'high risk' of recurrence might benefit from peri-operative systemic therapy. A recent retrospective analysis of patients with CRLM demonstrated only a clinical benefit on survival of neo-adjuvant systemic therapy in patients with a 'high clinical risk profile'.[29] However, it should be taken into account that in this study, patients who had disease progression during neo-adjuvant systemic therapy did not undergo liver surgery, and therefore the results from this retrospective analysis are biased. A randomised clinical trial (CHARISMA-trial) could answer the question whether 'high risk patients' benefit from additional systemic therapy before or after liver surgery.[30]

Pre-operative use of FDG-PET scan in patients with CRLM failed to select patients who were unlikely to benefit from liver resection. Therefore the search for new imaging techniques that can select patients, who are the wright candidates for liver surgery, continues. The optimal imaging technique should be able to diagnose small liver metastases, which might be responsible for early recurrences after liver surgery. One of these promising techniques might be diffusion-weighted magnetic resonance imaging (MRI) combined with gadoxetic acid –enhanced MRI, which has a high sensitivity in the detection of small (<1cm) liver metastases (CRLM as well as non-CRLM), as described in a recent meta-analysis.[31] Other imaging techniques such as perfusion CT imaging also are promising new techniques that need further research.[32]

A more extensive histopathological evaluation of CRLM might become important. Not only to identify prognostic factors for survival, but also in potential patient selection for adjuvant systemic therapy. In primary CRC, histological factors (e.g. extramural venous invasion, perineural growth, angioinvasion, lymphatic invasion and diffuse growth patterns) have been associated with poorer survival outcomes.[33,34] Especially extramural venous invasion is a poor prognostic factor and as a result, patients with stage II colon carcinoma in combination with extramural venous invasion are candidates for adjuvant systemic therapy.[35] Whether

these, or other histopathological factors are important for patient selection for adjuvant systemic therapy in case of CRLM has to be studied.

In anticipation of the results of many studies conducted for patients with liver metastases, it remains of utmost importance that these patients are referred to, or at least discussed with liver specialist centers. Multidisciplinary treatment of patients with liver metastases, either colorectal or non-colorectal, is the patients' only chance to receive the best, most up-to-date and tailored treatment.

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CHAPTER 11

Samenvatting van dit proefschrift en toekomstperspectieven

Samenvatting van dit proefschrift

De incidentie van levermetastasen en lever resectie

Veel patiënten met een maligniteit presenteren zich met levermetastasen, daarnaast ontwikkelen veel patiënten levermetastasen tijdens het beloop van hun ziekte. Kennis over de herkomst van deze levermetastasen is belangrijk voor patiënten, zeker voor patiënten die zich presenteren met metastasen zonder bekende primaire tumor.

In ***hoofdstuk 2*** werden meer dan 23.000 patiënten met histologisch bevestigde levermetastasen geanalyseerd gedurende een periode van 10 jaar (2001-2010). Via de PALGA database (een nationaal registratie netwerk voor cyto- en histopathologie in Nederland) werden de demografische gegevens van deze patiënten en de kenmerken van de primaire tumor verzameld. Colorectaal carcinoom (CRC) was de meest voorkomende primaire tumor locatie in patiënten met levermetastasen (35%), hoewel dit percentage een onderschatting zou kunnen zijn, aangezien er niet altijd een lever biopt zal worden afgenomen bij CRC patiënten met een verdachte afwijking in de lever. Vaak zal begonnen worden met systemische therapie zonder histologische bevestiging.

In deze studie werden levermetastasen vaker gezien bij mannen (53%), waarbij primaire tumor locaties zich voornamelijk bevonden in de long (plaveiselcel carcinoom) of in het colon/rectum. De meerderheid van de patiënten met levermetastasen was ouder dan 50 jaar (90.2%), hoewel levermetastasen van het mammacarcinoom en gynaecologische maligniteiten (plaveiselcel carcinoom en neuroendocriene tumor) relatief vaker voorkwamen bij vrouwen onder de 50 jaar. Levermetastasen van urologische en pulmonale (plaveiselcel carcinoom) origine kwamen vaker voor bij oudere mannen (>70 jaar).

Dit ruime overzicht aan primaire tumor locaties van levermetastasen (inclusief tumor type, geslacht en leeftijd) vormt een basis voor verder onderzoek en zou gebruikt kunnen worden in de ontwikkeling van diagnostische en follow-up strategieën.

De meerderheid van deze 23.000 patiënten, beschreven in ***hoofdstuk 2***, ondergingen alleen een lever biopsie, terwijl iets meer dan 3.900 patiënten een lever resectie ondergingen. ***Hoofdstuk 3*** beschrijft deze patiënten die een lever resectie ondergingen in Nederland tussen 2001 en 2010. Zoals kon worden verwacht, werd een lever resectie het meest frequent uitgevoerd voor patiënten met colorectale lever metastasen (CRLM) (88% van alle patiënten die een lever resectie ondergingen). Gedurende de studie periode werd er een significante stijging gezien in het aantal lever resecties dat per jaar werd uitgevoerd voor CRLM. Deze stijging kan gedeeltelijk verklaard worden door een stijging in de incidentie van primair CRC, echter een andere verklaring zou kunnen zijn dat de indicaties voor lever chirurgie zich uitbreiden. Een stijging van de leeftijd van de patiënten ten tijde van de lever resectie en een stijging in het aantal lever resecties voor multipele levermetastasen geven een aanwijzing in deze richting.

Niet-colorectale levermetastasen

Uit de data van ***hoofdstuk 2*** bleek dat bijna de helft van alle (histologisch bevestigde) levermetastasen afkomstig waren van niet-colorectale tumoren. De meest voorkomende primaire tumoren in deze groep waren: pancreascarcinoom, longcarcinoom, mammacarcinoom en melanoom. Ondanks het feit dat bijna de helft van de levermetastasen afkomstig was van niet-colorectale tumoren, was het aantal patiënten dat hiervoor een resectie onderging laag en steeg dit aantal ook niet (significant) gedurende de studie periode, zoals beschreven staat in ***hoofdstuk 3***. Er zijn een aantal factoren te bedenken die waarschijnlijk van invloed zijn op dit lage aantal, te weten: het ontbreken aan adequate follow-up om de levermetastasen in een vroeg stadium te kunnen diagnosticeren, een klein aantal patiënten dat daadwerkelijk resectabele levermetastasen heeft en het gebrek aan bewijs dat lever chirurgie überhaupt de overleving van patiënten met niet-colorectale levermetastasen verbeterd. Toch onderging een klein aantal van deze groep patiënten een lever resectie met als doel de overleving te verbeteren.

In ***hoofdstuk 4*** werden alle patiënten met gemetastaseerd mammacarcinoom naar de lever die een lever resectie ondergingen (*n*=32) in Nederland tussen 1994 en 2010 bestudeerd. In deze uiterst geselecteerde groep patiënten werd een mediane overleving gevonden van 55 maanden. De factoren in deze studie die geassocieerd bleken met een verbeterde overleving waren: een oestrogeen receptor positieve primaire tumor, een solitaire levermetastase en een unilobulaire lokalisatie van de levermetastasen.

Hoofdstuk 5 beschrijft alle patiënten in Nederland die tussen 1994 en 2010 een leverresectie ondergingen voor gemetastaseerd melanoom (*n*=32). In deze, wederom, uiterst geselecteerde groep patiënten was de mediane overleving 29 maanden. Deze resultaten zijn conform de eerder beschreven overlevingscijfers, vaak afkomstig vanuit 'single-center' studies, en wekken de suggestie dat een lever resectie geassocieerd is met een verbeterde overleving in patiënten met gemetastaseerd melanoom.[1-6] Factoren die in deze studie geassocieerd bleken met een verbeterde overleving na lever resectie waren: een solitaire levermetastase, unilobulaire lokalisatie en een beperkte lever resectie.

Bij patiënten met niet-colorectale levermetastasen is van belang om juist dié patiënten te selecteren die profijt hebben van leverchirurgie. Factoren die geassocieerd zijn met een verbeterde overleving zijn beschreven, maar variëren tussen studies. In patiënten met levermetastasen van gemetastaseerd mammacarcinoom zijn de volgende prognostische factoren het meest beschreven: oestrogeen receptor status van de primaire tumor[1,7,8], het aantal levermetastasen[7,8], en vrije resectie marges[9,10]. Bij patiënten met levermetastasen van een gemetastaseerd melanoom werden vrije resectie marges[5,6,11,12], het aantal levermetastasen

[4,6], en de lengte van het ziektevrije interval tussen behandeling van het primaire melanoom en de diagnose van de levermetastasen [4,5,12,13] het meest frequent beschreven als factoren die geassocieerd zijn met verbeterde overleving. Echter, deze factoren zijn afkomstig uit kleine cohort studies wat kan leiden tot een hoog risico op bias, daarom kunnen deze factoren meegenomen worden in de beoordeling van individuele patiënten, maar mogen zij niet gebruikt worden om patiënten lever chirurgie te ontzeggen.

Colorectale levermetastasen

Bijna 40% van alle CRC patiënten ontwikkelen CRLM, terwijl maar een klein aantal van deze patiënten leverchirurgie ondergaat, ondanks dat het totale aantal lever resecties toeneemt over de jaren. In ***hoofdstuk 3*** werd geschat dat ongeveer 20% van de patiënten met CRLM in Nederland een lever resectie ondergingen, wat overeenkomt met de internationale literatuur.[14,15] Een deel van het probleem is de beoordeling van de resectabiliteit van de levermetastasen, naast het feit dat niet alle patiënten met levermetastasen worden verwezen naar een lever chirurg ter beoordeling van eventuele chirurgische behandel opties.

In ***hoofdstuk 6*** werden 56 CT scans van patiënten met CRLM die behandeld werden met (palliatieve) systemische therapie (zonder resectie) in twee Nederlandse multicenter gerandomiseerde klinische studies herbeoordeeld door 3 ervaren leverchirurgen. Bij 16 patiënten (29%) was er geen overeenstemming of de CRLM resectabel, danwel niet-resectabel waren. Twee eerdere studies toonden al aan dat de besluitvorming bij patiënten met CRLM erg variabel is, zelfs tussen ervaren leverchirurgen.[16,17] Beide studies beschrijven een meningsverschil tussen leverchirurgen bij het beoordelen van de resectabiliteit van CRLM in bijna de helft van de patiënten.[16,77] Dit benadrukt de heterogeniciteit van de oncologische chirurgie, waarbij de besluitvorming rondom patiënten met CRLM wordt beïnvloed door de ervaring van de behandelende artsen (colorectale chirurg, leverchirurg en medisch oncoloog) en door de beschikbaarheid van de verschillende behandelopties (zoals inductie chemotherapie, lever resectie in twee stadia, vena porta embolisatie en de verschillende ablatieve technieken). Deze grote hoeveelheid aan behandelopties voor patiënten met CRLM zorgt ervoor dat er een multidisciplinaire aanpak noodzakelijk is.

In het tweede deel van de studie in ***hoofdstuk 6*** werd de overleving vergeleken tussen patiënten met CRLM die behandeld werden met (palliatieve) systemische therapie of een lever resectie ondergingen. De patiënten die werden behandeld met systemische therapie en na herbeoordeling van de CT-scan door alle 3 de leverchirurgen als resectabel werden afgegeven werden geïncludeerd. Deze 36 patiënten werden gematched (voor geslacht, leeftijd, en klinische risico score volgens Fong et al.[18]) met vergelijkbare patiënten die een leverresectie ondergingen. De patiënten die een resectie ondergingen hadden een significant betere overleving in vergelijking met de overleving van de patiënten die alleen met systemische therapie behandeld werden (56 versus 26.5 maanden). Op basis van de

resultaten van deze studie, moet lever resectie als de gouden standaard worden beschouwd voor de behandeling van patiënten met CRLM.

Prognostische factoren

In ***hoofdstuk 7*** werd de waarde van de fluorine-18-deoxyglucose positron emissie tomografie scan (FDG-PET scan) onderzocht, om deze mogelijk te kunnen gebruiken voor de preoperatieve patiënten selectie. De overleving van patiënten met CRLM die een preoperatieve FDG-PET scan (*n*= 206) ondergingen werd vergeleken met de overleving van patiënten zonder FDG- PET scan (*n= 407*). De resultaten toonden geen meerwaarde van de preoperatieve FDG-PET scan voor de patiënten selectie, aangezien de patiënten met een preoperatieve FDG-PET scan na lever chirurgie geen verbeterde ziektevrije overleving (DFS) (mediaan 17 versus 14 maanden) of overall overleving (OS) (mediaan 64 versus 54 maanden) hadden ten opzichte van patiënten zonder FDG-PET scan. Moulton et. al. evalueerden de veranderingen in behandelplan na een preoperatieve FDG-PET scan in patiënten met CRLM waar een lever resectie gepland was.[19] In slechts 2.7% werd het behandelplan gewijzigd naar aanleiding van de FDG-PET scan. Dit maakt dat een FDG-PET scan niet standaard deel uit hoeft te maken van de preoperatieve work-up van patiënten met CRLM.

Gedurende de laatste jaren is de prognose van patiënten met CRLM die een lever resectie ondergaan sterk verbeterd, met een 5-jaars overleving van meer dan 50%.[20] De zoektocht naar nieuwe prognostische factoren gaat echter onverminderd door, omdat deze relatief hoge overlevingscijfers helaas niet voor iedere patiënt met CRLM gelden. Sommige patiënten hebben een vroeg recidief wat leidt tot een verslechterde overleving.[20]
In ***hoofdstuk 8*** beschreven wij een literatuur studie naar histopathologische factoren die van invloed kunnen zijn op de overleving van CRLM patiënten na lever resectie. Voorbeelden van deze mogelijke factoren zijn: intrahepatische verspreiding van tumorcellen, resectie marges en tumor respons op neo-adjuvante systemische therapie. De meta-analyse toonde een correlatie tussen OS en vena porta en lymfatische invasie van tumor cellen en tussen OS en de resectiemarge. De meeste studies werden echter uitgevoerd in heterogene patiënten populaties. Om deze reden werden in ***hoofdstuk 9*** (retrospectief) patiënten geselecteerd met een solitaire CRLM, die niet neo-adjuvant behandeld werden en waar een sufficiënte follow-up beschikbaar was. In totaal werden 124 lever resectie preparaten opnieuw beoordeeld door twee onafhankelijke onderzoekers. De histologische factoren waar naar gekeken werd met behulp van hematoxyline-eosine kleuring (HE) waren: tumor-dikte op de overgang van metastase naar normaal lever weefsel en de aanwezigheid van een kapsel rondom de metastase. Intrahepatische vasculaire, lymfatische en galganginvasie

en perineurale groei werden geïdentificeerd met behulp van immunohistochemie. Naast deze histopathologische factoren werden de factoren uit de klinische risico score van Fong et al. verzameld (grootte van de metastase, het CEA, de lymfklierstatus van de primaire tumor en het interval tussen de behandeling van de primaire tumor en de diagnose van de levermetastase).[18] Intrahepatische lymfvat invasie van tumorcellen was de enige onafhankelijke negatieve prognostische factor bij patiënten met een solitaire CRLM, zeker wanneer er ook nog sprake was van intrahepatische vasculaire invasie. Deze combinatie zou een expressie kunnen zijn van een agressieve tumor. De waarde van lymfatische invasie als een negatieve prognostische factor moet verder onderzocht worden in patiënten die neo-adjuvant behandeld zijn, of die meerdere levermetastasen hebben.

Toekomst perspectieven

In 2014 is er een landelijk screeningsprogramma gestart voor colorectaal carcinoom(CRC) in Nederland, zodat de primaire tumoren hopelijk in een vroeg stadium opgespoord kunnen worden. De identificatie van asymptomatische patiënten met CRC zal hopelijk resulteren in een afname van patiënten met CRLM en daarmee de noodzaak tot leverchirurgie.
Echter, door het verbreden van de indicaties kan verwacht worden dat de toename van lever resecties de komende jaren zal continueren. In dit proefschrift zien we bijvoorbeeld dat oudere leeftijd geen contra-indicatie meer is voor lever chirurgie, wat ook in andere studies naar voren komt.[21,22] Co-morbiditeit en klinische conditie blijven belangrijk in de patiënten selectie, maar in de leverchirurgie is vooral het volume van de 'rest lever' van belang. Methoden om de rest lever te vergroten zijn embolisatie van de vena porta (PVE) en ligatie van de vena porta (PVL). Door het induceren van lever hypertrofie in het 'niet geëmboliseerde' lever deel, neemt het lever volume over het algemeen toe. Na ligatie of embolisatie van de vena porta moeten patiënten enkele weken wachten tot de lever hypertrofie optreedt, terwijl in de tussentijd ook progressie van de levermetastasen (in het 'niet-geëmboliseerde' lever deel) kan worden geïnduceerd. Een nieuwe techniek die dit probleem aanpakt is 'Associating Liver Partion and PVL for Staged hepatectomy' (ALPPS). Als eerste stap vindt bij deze procedure een transectie van het leverparenchym plaats (waarbij het wel in situ blijft), wordt de rest-lever tumor-vrij gemaakt (in het geval van bilobulaire ziekte) en vindt vena porta ligatie plaats. Na een wachtperiode van 1 tot 2 weken wordt de patiënt opnieuw geopereerd en wordt het leverdeel waar de porta geligeerd is, verwijderd. Na ALLPS wordt een grotere toename van het volume van de rest lever gezien dan na PVE of PVL, en was er minder tijd nodig tot de lever hypertrofie optrad.[23] ALPPS lijkt een veelbelovende techniek, maar na ALLPS wordt een hoge morbiditeit, mortaliteit en een verhoogde kan op vroege recidieven gerapporteerd.[24] Een gerandomiseerde klinische studie die ALLPS vergelijkt met een lever

resectie in twee stadia wordt momenteel uitgevoerd in Oostenrijk (NCT02758977) en zal de klinische effecten van beide technieken evalueren.

Lever resectie bij CRLM patiënten zal alleen uitgevoerd worden, indien een complete resectie (R0) kan worden bereikt. Deze benadering verdient mogelijk enige aanpassing nadat Ayez et al. gelijke lange termijn resultaten beschreven bij CRLM patiënten die een R0 resectie ondergingen en patiënten die een microscopisch niet radicale resectie (R1) ondergingen nadat zij neo-adjuvant behandeld waren.[25] Andere patiënten met vergevorderde levermetastasen hebben soms zo'n goede respons op neo-adjuvante systemische therapie dat een aantal levermetastasen verdwijnen en alleen de zichtbare metastasen verwijderd worden.[26] Deze patiënten kunnen een lange termijn overleving hebben, waarbij de vraag rijst of chirurgische therapie als aanvulling op deze systemische therapie overlevingswinst geeft voor patiënten met meerdere, niet-resectabele colorectale metastasen (lever en ook andere locaties). De ORCHESTRA trial (NCT01792934) is opgezet voor deze groep patiënten met niet-resectabele colorectale metastasen en randomiseert tussen maximale dubulkings-chirurgie en het continueren van systemische therapie. De resultaten van deze studie moeten worden afgewacht, maar kunnen er potentieel toe leiden dat debulkings-chirurgie een belangrijke behandel optie gaat worden bij patiënten met niet-resectabel stadium IV CRC.

In dit proefschrift werden patiënten die neo-adjuvant behandeld waren geëxcludeerd in de verschillende studies, omdat het beoogd was een homogene groep patiënten te bestuderen. Neo-adjuvante therapie kan mogelijk de overleving van patiënten verbeteren, maar zou ook de prognostische factoren na chirurgie kunnen beïnvloeden. De rol van perioperatieve systemische therapie voor patiënten met primair resectabele CRLM werd recent beschreven door Nordlinger et al., en toonde geen overlevingswinst na 7 jaar follow-up.[27,28] In deze studie werden patiënten echter niet ingedeeld in risico categorieën en het zou zo kunnen zijn dat alleen patiënten met een 'hoog risico' baat hebben bij perioperatieve systemische therapie. Een recente (retrospectieve) analyse van patiënten met CRLM toonde alleen een klinisch voordeel van neo-adjuvante systemische therapie bij patiënten met een 'hoog risico profiel'.[29] Echter, in deze studie ondergingen de patiënten met progressieve ziekte onder de neo-adjuvante systemische therapie geen leverchirurgie wat zorgt voor bias in de resultaten van deze retrospectieve studie. Een gerandomiseerde klinische studie (CHARISMA-studie) zal de vraag moeten gaan beantwoorden of 'hoog risico patiënten' baat hebben bij (neo) adjuvante systemische therapie rondom leverchirurgie.[30]

Het preoperatieve gebruik van een FDG-PET scan bij patiënten met CRLM bleek een ongeschikt middel om patiënten te selecteren die mogelijk geen baat hebben bij leverchirurgie. De zoektocht naar nieuwe beeldvormingstechnieken die wel in staat zijn de juiste patiënten

voor lever chirurgie te selecteren gaat verder. De optimale beeldvormingstechniek moet in staat zijn kleine levermetastasen te detecteren die mogelijk de oorzaak zijn van een vroeg recidief. Één van deze veelbelovende technieken is de diffusie MRI gecombineerd met gadoxetine zuur. Deze techniek heeft een hoge sensitiviteit voor wat betreft de detectie van kleine levermetastasen (<1cm) (CRLM en niet-colorectale metastasen), zoals beschreven in een recente meta-analyse.[31] Andere technieken, zoals perfusie CT scan zijn eveneens veelbelovend en verdienen verder onderzoek.[32]

Uitgebreidere histopathologische evaluatie van CRLM zou belangrijker kunnen worden. Niet alleen om prognostische factoren te identificeren, maar potentieel ook voor de patiënten selectie voor adjuvante systemische therapie. Bepaalde histologische factoren (zoals extramurale veneuze invasie, perineurale groei, lymfatische invasie en een diffuus groeipatroon) zijn geassocieerd met slechtere overleving in patiënten met primair colorectaal carcinoom.[33,34] Vooral extramurale veneuze invasie is geassocieerd met een slechte prognose, om deze reden zijn patiënten met stadium II coloncarcinoom in combinatie met extramurale veneuze invasie kandidaten voor adjuvante systemische therapie.[35] Of deze, danwel andere histopathologische factoren eveneens belangrijk zijn in de patiënten selectie voor adjuvante behandeling voor CRLM is een vraag die verder onderzoek nodig heeft.

In afwachting van de resultaten van de vele studies die momenteel uitgevoerd worden voor patiënten met levermetastasen, blijft het van het grootste belang dat deze patiënten verwezen worden naar, of op zijn minst besproken worden met, een specialistisch levercentrum. Een multidisciplinaire behandeling van patiënten met levermetastasen (zowel colorectaal als niet-colorectaal) is de enige kans voor deze patiënten op de beste 'behandeling op maat' met de meest moderne inzichten.

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Curriculum Vitae

Dankwoord

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Curriculum Vitae

Jannemarie de Ridder was born on the 3rd of November 1982 in Woudenberg (Utrecht), the Netherlands. After graduating from Ichthus College in Veenendaal, she started medical school in 2001 at Radboud University Nijmegen, where she graduated in 2008.

After finishing medical school she worked for a year at an emergency department at Gelre Hospital, location Zutphen, where she decided to focus on surgery. In 2010 she started working at Radboud University Medical Center, which laid the foundations for this thesis with help of prof. dr. JHW de Wilt and prof. ID Nagtegaal. The results of the studies were presented at national and international meetings.

She started her surgical training in 2013 at Radboud University Medical Center (prof.dr. CJHM van Laarhoven and dr. B Verhoeven). Her training continued at Elisabeth Tweesteden Hospital in Tilburg, under the supervision of dr. PWHE Vriens and dr. MS Ibelings. She will continue her surgical training to become a vascular surgeon in Tilburg (dr. PWHE Vriens).